THE JOURNAL
OF
MENTAL SCIENCE
(THE BRITISH JOURNAL OF PSYCHIATRY)

BY AUTHORITY OF
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VOL. CI

LONDON
J. & A. CHURCHILL, LTD
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MADE AND PRINTED IN GREAT BRITAIN BY
HEADLEY BROTHERS LTD
109 KINGSWAY LONDON W C 2 AND ASHFORD KENT

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THE
JOURNAL OF MENTAL SCIENCE
[*Published by Authority of the
Royal Medico-Psychological Association*]

No. 422 [NEW SERIES NO. 386.] JANUARY, 1955 VOL. 101

Original Articles

THE CONTRIBUTION OF PSYCHOLOGICAL MEDICINE TO GENERAL MEDICINE

THE PRESIDENTIAL ADDRESS DELIVERED AT THE ONE HUNDRED AND THIRTEENTH ANNUAL MEETING OF THE ASSOCIATION ON WEDNESDAY, 14 JULY, 1954

By

NOEL G. HARRIS, M.D., F.R.C.P., D.P.M.

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I DEEPLY appreciate the honour that the Royal Medico-Psychological Association has paid me in electing me President for this Year.

It is a tribute to the Middlesex Hospital and to all those who have worked with me, and who are now working with me in the Department of Psychological Medicine.

I shall strive to justify the confidence that the Association has placed in me by making me President, and I shall do my best to uphold the high tradition of my predecessors.

It is a particular pleasure to me to be inducted here at St. Luke's-Woodside, not only because of my close association with this Hospital since 1935, but also because of the part that Physicians connected with St. Luke's in earlier years have played in the history of the Royal Medico-Psychological Association and Psychiatry. I hope that a brief account of this will be of interest, and will explain how St. Luke's-Woodside became the Psychiatric In-patient Wing of the Middlesex Hospital.

Royal Bethlem is the oldest Mental Hospital in England. I believe the second oldest is Bethel Hospital, Norfolk.

On 13 June, 1750 "Six charitable gentlemen of the City of London met in the King's Arms Tavern in Exchange Alley to consider the establishment of a hospital for the care and treatment of poor lunatics". (1) As a result of this meeting, St. Luke's Hospital was opened in 1751. It is of interest that the first physician to St. Luke's was Dr. William Battie, who in 1764 was elected President of the Royal College of Physicians.

At this point I should like to record that in 1766 the Manchester Lunatic Hospital was opened by the Trustees of Manchester Infirmary and this eventually became Cheadle Royal Hospital.

In 1914, when St. Luke's Hospital was still in Old Street, the site was sold to the Bank of England. The old Hospital was finally closed in 1917.

After the first World War the Governors decided not to build another Mental Hospital, but at the suggestion of Dr. R. W. Gilmour, who had been Assistant Medical Officer at St. Luke's, and who was in close consultation with Sir Hubert Bond, one of the Commissioners of the Board of Control and President of the Royal Medico-Psychological Association in 1921, the Board decided to approach the Middlesex Hospital with the idea of starting a Psychiatric Out-patient Clinic there. Not only was this arranged, but provision was also made for the use of six beds in the Neurological Ward of the Middlesex Hospital for suitable psychiatric cases, the cost and maintenance of these beds being borne by St. Luke's. This agreement came into action in 1923, with Dr. R. W. Gilmour responsible both for the Out-patient Clinic and ward cases.

This appears to be the first occasion on which a Teaching Hospital has allocated beds for psychiatric illness, since the closing of the "Lunatic Ward" at Guy's Hospital in 1860.

Soon after this arrangement with The Middlesex, the Board of Governors of St. Luke's considered the question of further building, and in 1930 opened Woodside as a Hospital for functional nervous disorders in the educated classes.

At the outbreak of the second World War Woodside Hospital was allocated by the Government as a Hospital for officers suffering from psychiatric disabilities.

Patients were admitted from any of the allied services. There was accommodation for patients of both sexes so that altogether during the war officers from twenty-five different services were admitted.

With the formation of the national health service, it was decided that the Middlesex Hospital and St. Luke's Ancient Foundation should amalgamate completely, and the Board of Governors of the Middlesex Hospital decided to utilize Woodside, which was re-named St. Luke's-Woodside, as its in-patient psychiatric wing.

You will realize, therefore, that those of us who are fortunate enough to work here not only have the old heritage of St. Luke's Foundation, but also all the advantages of being part of a London teaching hospital.

In view of what has just been said I am sure that you will share with me the pleasure and thrill which I got when I found that this is the Centenary Year of the Presidency of the Royal Medico-Psychological Association, and that the first President elected in 1854 was Dr. A. J. Sutherland, who at that time was medical superintendent of St. Luke's Hospital, in Old Street.

With all this history behind me and considering that this annual meeting is being held in such close association with one of the London teaching hospitals, I felt that there could be no more appropriate theme for this address and annual meeting than that of "The Contribution of Psychological Medicine to General Medicine".

Firstly, I have endeavoured to obtain some factual information in order to show the extent to which the ill-health of the nation is caused by what for brevity I will call psychiatric or psychogenic disturbance. I am indebted to the Ministry of Health, the Board of Control and the Ministry of Pensions and National Insurance for their help in enabling me to obtain the following figures.

On 31 December, 1952 there were a total number of 149,353 patients in mental hospitals suffering from some type of mental disorder. On the same date there were 135,316 people suffering from mental deficiency who were in hospitals, on licence, under guardianship, under statutory supervision or voluntary supervision.

The number of mental hospitals, Section 20 hospitals, registered hospitals, licensed houses and nursing homes taking voluntary and temporary patients came to a total of 357, and in addition there was Broadmoor State Institution.

The number of mental deficiency hospitals, certified institutions, and approved homes, was 184. In addition there were Rampton and Moss Side State Institutions.

The cost to the nation of mental hospitals, state institutions and the Bethlem and Maudsley Hospitals, together with the salaries of specialists in the Mental Hospitals and Mental Deficiency Institutions is approximately £45,661,000 a year.

There are no data, other than those mentioned above, by which we can estimate the cost of upkeep of the numerous clinics, neurosis centres or beds for mental disorder or mental deficiency. It is possible that the cost of these scattered beds and units might amount to a further 5 per cent. of the total already mentioned.

It would appear from the statistics supplied by the Ministry of Pensions and National Insurance (2) that during the year 1950 the number of periods of absence from work for which insurance benefit was paid owing to psychological illness, i.e. the psychoses and neuroses was about 206,000 (involving a loss of something like 10 million days). During any one year the cost to the Nation of sick benefit for such an amount of incapacitating illness is approximately four and a half million pounds, which is about 5¼ per cent. of the total paid out during one year in sick benefit for all causes.

In addition to this group (the Psychoses and Psychoneuroses), it is interesting to note some of the other diagnostic labels used in this particular table of statistics. There are, for instance, such headings as:

(*a*) Allergic disorders:

Asthma
Urticaria
Other allergic disorders.

(*b*) Diseases of the stomach and duodenum, other than ulcer, cancer, gastritis and duodenitis.

(*c*) Diseases of menstruation.

(*d*) Diseases of the skin.

(*e*) Rheumatism, except rheumatic fever.

Under a main heading "Other unspecified and ill-defined diseases" there are sub-headings indicating symptoms referable to a number of the systems, e.g. cardiovascular, gastrointestinal and the abdomen. Nervousness, debility, and headache form yet another heading.

Remembering that these statistics are compiled from the medical certificates sent in by medical practitioners, it is interesting to conjecture in what percentage of the above groups psychogenic disturbance plays a big or the biggest part in the aetiology of the illness. It is not very popular among patients to have a medical certificate showing that their illness is psychogenic. It is not rash to assume that many of the medical certificates bearing such diagnoses as are covered by the above headings or such an ill-defined diagnosis as fibrositis, myalgia, neuralgia, rheumatism, or even gastritis, really cover an illness that is mainly psychogenic.

The clarification of this point is an eminently worth while piece of research work for someone to undertake.

In order to throw some further light on the incidence of psychogenic disturbance in association with what would appear to be primarily physical illnesses, I have approached the Heads of the Departments of Physical Medicine in the twelve London Teaching Hospitals. It is commonly said that more chronic patients gravitate to the Departments of Physical Medicine and Departments of Psychological Medicine than to any other departments. Even though the evidence that has been obtained from this enquiry is not factual, the experience and impressions of these twelve physicians is surely a definite guide to correct facts. I am most grateful to them for their help. Of the twelve departments, the information gained might be summarized in this form.

(1) Patients showing considerable psychogenic disturbance are seen in every one.
(2) Cases of pure psychiatric disorder are the exception.
(3) Many cases in which there is a physical basis have also associated psychological factors, and this fact it is important to consider.
(4) It is always important to look for the physical factor and not just to label a patient "functional".
(5) Assessments of the percentage of patients seen whose illness is mainly psychogenic varies from 10 per cent. to 30 per cent. In one department seeing 2,000 new patients per year 300 are referred to their psychiatric department, and in addition there are probably another 900 who have a very strong psychological element in the aetiology.
(6) The physician to one department writes "There are many patients who are suffering from misery and not pain" also "Minor organic disturbances become the basis for major anxiety".
(7) How best to treat the chronic patient, whose numbers ever tend to increase, used to present a real problem. It is very gratifying to learn that this problem is less in those departments in which the psychological sick is taken into account. Close co-operation with the psychiatric department is advised. One department has weekly resettlement conferences.

An interesting fact was brought to light by one observer, who informed me that, when working at one London teaching hospital, he carried out some investigations and found that since the end of the second world war the greatest increase in out-patients had occurred in the Departments of Physical Medicine and Psychiatry.

All this evidence leaves little doubt as to the size of the problem and contradicts the statements made or implied by those who still regard psychological medicine as a comparatively useless adjunct to general medicine.

I have not said much about the sufferings of the patient who is ill with some sort of psychogenic illness. Even today there are many medical people and lay people who are inclined to belittle the severity of psychogenic illness, yet those who have suffered from it, or have seen it daily face to face can have no doubt as to the suffering through which many such patients pass.

Perhaps the greatest contribution that psychological medicine has made, and still can make to general medicine, is by re-iterating the importance of emotion in considering the aetiology and treatment of many physical symptoms. Also the importance when treating a patient of taking into consideration not only the local pathological process, but the patient as an individual and how he reacts to his illness.

The importance of regarding the maintenance of health from many angles has been steadily increasing. The growth of the study of public health with its many view points has demonstrated this fact. It must not be forgotten that the improvement of general living conditions which has been attained by Public Health Authorities inevitably leads to people enjoying happier lives, and so, less emotional tension.

It has, of course, been known for many years that our physical state is affected by emotion, hence such common expressions as "My hair stood on end with fright". Only in recent years has the truth of these observations been applied in medicine in an attempt to understand more fully the aetiology of the many physical symptoms of which ill people complain, and to which up to the present some completely unsatisfactory diagnostic label has been applied, such as chronic rheumatism, fibrositis, myalgia, disordered action of the heart.

Moreover, the importance of what is perhaps best termed "emotional tension" in the aetiology of physical diseases, such as gastric ulcer, ulcerative colitis, asthma, skin affections of certain types, and some muscular and joint disturbances, is only just beginning to be appreciated.

I think perhaps the clinical experience that made me personally realize more than anything else the significance of emotional disturbance in affecting our physical state was the case in this hospital which was recorded by Dr. Robert Moody (3).

Some of those present may not have read of this case, the outlines of which are as follows:

An army officer of 33 years was admitted in 1943. The main presenting symptom was somnambulism. He was treated by abreactive methods, and on one occasion, after abreacting an incident which had occurred 10 years previously—an occasion when he had been lost in the jungle for some hours at night with his forearms bound tightly together—the complete marks of the ropes reappeared on the forearms. It was possible to repeat this on two further occasions under special conditions, in order to make certain that it was absolutely genuine, and to photograph the marks. Subsequently a number of similar phenomena have been observed in other patients.

How this occurs no one has any idea. It may be through a reactivation of some neuronic path from the skin, blood vessels, autonomic nervous system to cerebral tissue, including some hormonal activity.

The importance of studying such a phenomenon seems to lie in the possibility to demonstrate how emotion does affect the physical state. It is usually difficult to allay emotional tension. Certain drugs, such as sodium amytal, have a beneficial effect in a certain percentage of cases, but there are obvious disadvantages of patients going on taking large doses of any drug. Psychotherapy is the most rational form of treatment for the purpose of allaying emotional tension, but it is so often a long process and difficult to arrange, and it is by no means always a certain cure. If, therefore, it were possible to find the exact mechanism whereby emotion did affect the physical state, it might be possible to "block" the path by some means, and so free the patient from many of his most troublesome symptoms. Most of us hesitate to resort to leucotomy or allied surgical procedures unless the condition is very severe.

Admittedly this still leaves the problem, where and how is the emotion generated in the first place, and this calls for more research, and better prophylaxis. How often in psychological medicine one feels that the illness could have been easily prevented, whereas the cure is so hard.

The interesting and important research work being carried out by Professor G. W. Harris at the Maudsley Hospital and mentioned by him in the inaugural lecture given by him as Fitzmary Professor of Physiology, throws light on this whole problem. For many years it has been unknown how a baby extracts milk from the breast; it is probable that the power of sucking alone is not really sufficient to extract the milk present in the deeper parts of the breast tissue. It has been known that if a mother who is breast feeding her baby has become emotionally upset, the breast milk might appear to dry up so that the baby would not get sufficient.

It has recently been found that the sensory stimuli directly involved in suckling (and probably conditioned stimuli as well) cause the secretion of oxytocic hormone from the posterior pituitary gland which is carried in the bloodstream to the mammary gland, and there it causes contraction of the myoepithelial cells that surround the alveoli and ducts of the mammary gland. The milk is therefore actively expressed from the mother's breast to the child.

Moreover, there is strong evidence that this reflex activation of the posterior pituitary gland by suckling can be interfered with by emotional disturbance. This has been demonstrated by Newton and Newton (4), in the human female, and more recently by Cross (5) in Cambridge working with rabbits.

Further recent research work in Sweden (6) has shown that lactating women from whom their babies have been unable to obtain milk present in the breast tissue, profit by a single injection of oxytocic hormone at the time of suckling. It would seem that one good demonstration to the woman that she can give a large supply of milk to her child, restores her confidence and allays her anxiety so that at future suckling periods the reflex is established and suckling proceeds normally.

Increasing knowledge of electro-physiology, and the very special study of cybernetics may throw light on this whole question. Ashby in his article on "The Application of Cybernetics to Psychiatry" (7) points out that over-stability occurring in some portion of a dynamic system such as the brain, may render the whole action of the system functionally less effective. There is a fundamental law that, when a whole system is composed of a number of sub-systems, the one that tends to dominate is the one that is least stable. This statement is capable of mathematical proof, and holds over all mechanisms—nervous included. A clearer understanding of this fact might explain some of the puzzles concerned with the obsessional neuroses. The obsessional personality does seem to be constitutionally determined. Some of the characteristic features of the obsessional, such as conscientiousness, drive, methodicity, and aim for perfection all go to make for the stable efficiency of the individual, and yet if these characteristics get exaggerated, the cause of which might be some subtle change akin to the over-stability of the machine, the individual as a whole breaks down. This was often seen in the war, when the obsessional could not de-centralize, tried to do everything himself and, of course, wore himself out. Also there is evidence to suggest that it is the obsessional type of personality with repressed aggression who develops certain types of dermatological lesions.

I hope that the data obtained and the views expressed have been sufficiently convincing to leave no doubt in your minds as to the importance of psychological medicine making its contribution to general medicine.

If the best results are to be obtained our brother practitioners must help us by giving us the chance to make that contribution. Constructive criticism is helpful, but not bias, nor prejudiced and often ignorant ridicule.

These observations, then, lead me to the development of the speciality of psychological medicine and its teaching.

In 1808 the Justices of Quarter Sessions were given power to establish asylums. In 1845 this was made compulsory.

In 1888, by the Local Government Act the Councils of Counties and County Boroughs took over the administrative powers of the justices in this respect.

Apart from the asylums, there was little or no provision for beds for psychiatric disabilities, and up to 1930 the asylums were only allowed to admit certified patients. In addition to asylums, there were the colonies for mentally defective patients as well.

There was practically no provision for the treatment of milder psychiatric disorders.

In 1904 the Lady Chichester Hospital was opened for such cases by Dr. Helen Boyle. In 1921 the Cassel Hospital was opened for treatment with Dr. T. A. Ross in charge, and in 1930 Woodside Hospital was opened.

The provisions made for teaching psychological medicine have progressed slowly until recently.

On reference to the General Medical Council, to whom I am much indebted for their help, it was found that prior to 1885 apparently no official instruction had been issued by the General Medical Council that anything concerning mental diseases should be included in the medical curriculum.

On 1 July, 1880 the General Medical Council considered a letter dated 4 August, 1879 from the Hon. General Secretary of the Medico-Psychological Association. At that time the Hon. General Secretary was Dr. Henry Rayner of Hanwell, who later in 1884 became President of the Association. This letter stated that at the Annual General Meeting of the Medico-Psychological Association, under the Presidency of Dr. Lush, M.P., a resolution was passed petitioning the General Medical Council to have mental diseases made a subject of examination for all degrees and licences to practice medicine in the United Kingdom. To this letter the Council replied that mental diseases were already part of regular courses of instruction in medicine, but that they did not deem it expedient at present to ask licensing bodies to have mental diseases made the subject of separate examinations.

Nevertheless, in 1885, when considering recommendations in regard to professional education and examination the Council added mental disease as a separate item in the curriculum, thus making twelve main items, whereas previously there had been eleven.

There is also a further paragraph which reads "Professional examinations should then be so framed as to secure that the knowledge of every practitioner whose name appears in the Medical Register has been tested in all the subjects of professional education which the Council deem essential only".

It seems not out of place at this point to ask how, since 1885 to the present day, examiners have satisfied and do satisfy themselves that candidates have that knowledge, so far as psychological medicine is concerned?

The Royal College of Physicians have also been good enough to look up their records for me, and I am indebted to them for the following information: In 1932 David Forsyth in a paper entitled "The Place of Psychology in the Medical Curriculum" (8) pointed out that the training of medical students in psychology was almost nil. For the most part lectures and demonstrations on insanity were all that was considered necessary, and that was because of the regulations just mentioned. Forsyth also quotes Dr. C. A. Mercier, President of the Royal Medico-Psychological Association in 1908, who pointed out that all the instructions that a medical student got was how to recognize and certify an insane person.

Information concerning the development of psychiatry in the twelve London teaching hospitals had been gathered through the kind collaboration of my colleagues at each of the hospitals in question, and to them I am most grateful. It is, I suppose, obvious that teaching hospitals should exercise the greatest influence in training students in the right attitude of mind towards medicine. The extent to which this has been carried out so far as Psychology and modern concepts of psychological medicine are concerned has been very slight until in recent years.

From about 1850 to approximately 1920 there was only teaching of mental diseases. Charing Cross Hospital appears to have started teaching mental diseases in 1852, when Dr. Conolly was the lecturer. Dr. Conolly was President of the Royal Medico-Psychological Association in the year 1858. There was no department of psychological medicine, by which I mean the appointment of a physician for mental diseases to the staff, until 1902, when Dr. Percy Smith was appointed. Dr. Percy Smith was President of the Royal Medico-Psychological Association in 1904. Some students of St. Thomas's Hospital were sent to Hanwell Lunatic Asylum or Bethlem for instruction in 1849, and subsequent years.

In 1893 Dr. Rayner apparently saw out-patients at St. Thomas's, but he does not appear to have been on the staff.

The first appointment of this kind seems to have been in 1909, when Dr. R. Percy Smith, who in 1905 had resigned his position at Charing Cross in order to come to St. Thomas's, was appointed.

At King's College Hospital a chair in psychological medicine has existed since 1871, and the first Professor was Dr. Sheppard of Colney Hatch Asylum, but apparently his sole duties were teaching. The first physician for psychological medicine was Professor Mapother.

At Westminster Hospital, mental diseases were first taught during the course in forensic medicine in 1872. A Department was first formed in 1939, following a liaison with Springfield Mental Hospital.

At University College Hospital the first physician in mental diseases was Dr. Bernard Hart, who was appointed in 1913.

At St. Bartholomew's Hospital Sir Robert Armstrong-Jones seems to have been the first physician for mental diseases and his department was formed in 1919. Sir Robert Armstrong-Jones was President of the Royal Medico-Psychological Association in 1906.

St. George's Hospital first formed a department of psychological medicine in 1933 when Dr. Desmond Curran was appointed. Before that date there was simply "A Lecturer on Insanity".

At the Royal Free Hospital a department was started in 1943 under Dr. W. D. Nicol. The London Hospital formed a Department in 1942 under Dr. Henry Wilson, though in 1924 Dr. Millais Culpin had been appointed Lecturer in Psychoneuroses.

At Guy's Hospital the first course of lectures was given in the summer session of 1871, by Dr. Thompson Dickson. He was followed by Dr. G. H. Savage, who was appointed to the School in 1874. In 1896 Sir George Savage was appointed to the staff, this being the first staff appointment. Sir George Savage was President of the Royal Medico-Psychological Association in 1886.

The York Clinic, a tribute to the late R. D. Gillespie, was opened in 1944. It was the first Psychiatric Wing to be built in the grounds of an undergraduate teaching hospital. In 1932 Guy's opened their child guidance clinic.

At the Middlesex Hospital the first Lecturer was Dr. Henry Rayner, appointed in 1873. The department of psychological medicine was first formed in 1937 when I was appointed.

At St. Mary's Hospital the first lecturer appears to have been Dr. Crichton Browne in 1881. The first appointment of a physician for psychological medicine was Dr. Cole in about 1910.

These facts show that teaching on mental disorders for the purpose of diagnosis and disposal of the insane has been going on for many years. On the other hand it is only in recent years that much effort has been made to teach psychology and psychiatry, and to orientate that teaching towards the close connections that exist between general medicine and the numerous psychological factors that enter into the study of aetiology. At the present time, however, every London Teaching Hospital has a department of psychological medicine, progressive teaching is going on, and in several of these hospitals there is an allocation of beds for psychiatric cases.

The importance of the personal relationship between the patient and those who are looking after him in his illness, has been mentioned. It is recognized that many of those, who are engaged in medical and nursing practice, have a natural gift of sympathy and understanding, and that their relationship with their patients is all that can be desired, yet this is by no means always the case. Surely all increase of knowledge should be used and tried out, so is there any justification for not teaching psychology in order to see if it does improve these personal relationships? Psychology should not be regarded as a part of the speciality of psychiatry, but as a basic subject in the medical curriculum as are anatomy and physiology, which should be taught to students in order to enable them to gain the fullest possible knowledge of the human individual. The need for stressing the importance of this personal relationship is particularly strong at present with the advent of the National Health Service and the fears of many that the treasured tradition of the family doctor may be lost.

The importance of understanding the relationship that undoubtedly exists between the physical changes and our emotional life has also been stressed. In order to increase our knowledge concerning this problem, a closer cooperation between all those concerned is essential, and I venture to ask for an even greater change of attitude towards these problems.

Perhaps I may be forgiven for mentioning the Middlesex Hospital where I have been so fortunate in the support of my colleagues. In 1936 lectures in psychology were started to the second and third year medical students during the course on physiology. This was made possible by the foresight and cooperation of Professor Samson Wright, and the approval of the Dean, Sir Harold Boldero. Since that time lectures have been given in applied medical psychology, in the introductory course of the medical unit. For some years lectures on psychology have also been given to nurses and to physiotherapists as well as those to medical students. Since the amalgamation a regular flow of nurse probationers has been sent up from the Middlesex Hospital for a period of three months to nurse at St. Luke's-Woodside, and recently a scheme has been introduced with the official approval of the General Nursing Council, whereby a qualified nurse can put in nine months at St. Luke's-Woodside, followed by nine months at Shenley Hospital, and then take the examination for the mental nursing certificate.

Thus, over a period of eighteen years the teaching of psychology at the Middlesex has been steadily increasing, I feel that this would not have been allowed to continue had it not been for the benefit of all students.

I have been in a particularly fortunate position for observing the results of teaching to medical and other students. From 1923 to 1935 I was teaching nurses in a county mental hospital. In 1923 there was no sister tutor, and it was necessary to teach not only the subjects required for the nursing certificate, but practical bedside nursing, which meant learning a lot of it oneself if one was to attempt to teach and demonstrate it. This gave one an exceptional opportunity of combining the teaching of medical psychology with the general and mental nursing. I would like to put on record here how magnificently the nurses, both male and female, responded. It certainly showed how nurses will respond if only the medical staff will work with them as a team, and I cannot stress the importance of physician, nurse, occupational therapist, psychiatric social worker, psychologist and others working as a team. If the team spirit is right and the co-operation really close, I believe that nothing but good can come of it. Some critics say that it interferes with the analytical treatment or that professional secrecy is endangered. I believe that if the team spirit is wisely directed, such difficulties can be overcome.

Moreover, I have been closely associated with the teaching of psychological medicine in two other London Teaching Hospitals in addition to the Middlesex. At St. Thomas's Hospital I had the privilege of helping Dr. Henry Yellowlees, from whom I learnt so much and to whom I owe a great deal.

I also took part in the teaching of medical students from Westminster Hospital.

Thus, with all humility, I feel that this experience has given me the opportunity to assess the value of teaching psychology and psychiatry to undergraduates.

Tomorrow we shall hear the best ways in which such teaching should be carried out.

The progress made in teaching along these lines has developed quickly since the war and is still doing so. I was delighted to read in Sir John McNee's Presidential Address to the British Medical Association (9) "The Teaching Hospitals are mainly concerned with the training of our future doctors (and also doctors returning for further experience) but it is often forgotten that doctors are responsible, in part at least, for the training of nurses, almoners, dietitians, physiotherapists, radiographers and laboratory technicians of many kinds". I was grieved, however, to read no mention of the importance of considering the individual's emotional life, and only once in that otherwise excellent address was the word "psychology" mentioned.

The responsibility rests on us who specialize in psychiatry to convince the rest of the profession of the reality of our claims. If we are going to do this successfully, it is essential to make it clear that our knowledge on these matters is still in its infancy, not to claim too much, not to make dogmatic statements which cannot subsequently be justified. We must avoid prejudice and bitter disagreement amongst ourselves. So long as theories and practice are put forward in an honest desire for knowledge and progress, let them be considered fairly, and let this be criticized not only destructively, but constructively.

I hope that the papers which are to be read tomorrow and subsequently will help to carry forward not only progress in our own speciality, but in general medicine as well.

In these days it is necessary not only to have the efforts of the individual but the force of combined operation such as a united society gives. Who better than the Royal Medico-Psychological Association can see to it that this much desired end is attained?

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NICOTINIC ACID MODIFIED LYSERGIC ACID DIETHYLAMIDE PSYCHOSIS*

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(Received 29 June, 1954)

INTRODUCTION

THEORETICAL models ranging from neurological to analytical have been introduced in the hope of providing new insights into psychopathology. The flesh and blood model is of more recent origin in this field. The experimental or model psychosis results from giving "normals" drugs which bring about a psychotic-like experience for a few hours. As is the case with theoretical models, the flesh and blood models are not accurate representations of the naturally occurring psychosis. In fact, the variability manifest in most naturally occurring psychoses makes the existence of an accurate model impossible. A model, whether carefully planned and developed or accidentally discovered, is useful to the extent that it assists us in better understanding the naturally occurring process it approximates. It is useful if it enables us to set up and test hypotheses which contribute additional knowledge about disease aetiology, mechanisms, or treatment. The model psychosis to be studied in this paper is that produced by lysergic acid diethylamide (LSD).

When LSD became available for psychiatric study, it spurred anew correlative biochemical and psychological investigations. Many authors (1, 2, 3, 4) have reported using LSD to produce experimental psychoses, as an aid to psychotherapy, as an euphoriant and as a diagnostic adjunct. This amazing compound is effective in gamma (·001 mgm.) dosages compared to mescaline which is used in 0·3–0·5 gram dosages. The mescaline and LSD phenomenon have been compared with toxic and acute florid schizophrenic psychoses.

For the purpose of this study we assume this model psychosis in some ways approximates to the naturally occurring phenomena known as schizophrenia. To outline a systematic argument for the similarity between the model selected and schizophrenia will not be undertaken here for various reasons; one reason being that no generally acceptable systematic description of schizophrenia has been made and we doubt our own ability to do it. Another reason is that the value of the model will be judged initially by its ability to help develop testable hypotheses. Thus, knowing the pharmacology of LSD, the compound which produces the model psychosis, and knowing the symptoms that "normal" subjects commonly develop when the compound is administered, our task is to develop a hypothesis about the modification of this model psychosis and to run a pilot project built around the hypothesis developed. The structure of LSD is as follows:

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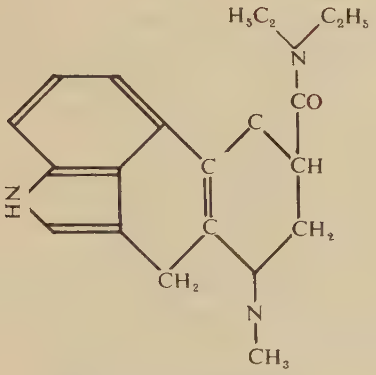
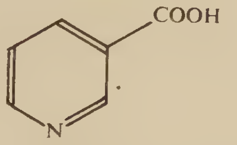


Lysergic Acid Diethylamide

In looking for a means of modifying its effects, we can think in terms of chemical modification through competitive inhibition by structural analogues. Thus, we should look for a chemical similar in structure to LSD as one criteria.

Further, some work has been done on the possible action of LSD which should be considered. Mayer-Gross (5, 6) has made the assumption, and presented some evidence in support of it, that LSD interferes with carbohydrate intermediary metabolism. Similarly, Schueler (7) reported that in four cases administrations of sodium succinate rapidly removed most of the effects of mescaline from their research subjects. Thus, another criterion in looking for a compound to modify the LSD action would be one that facilitates carbohydrate intermediary metabolism.

Finally, the LSD psychosis has been compared to both toxic and functional psychoses. In surveying compounds which have proven useful in the treatment of the above conditions, and which met the two requirements previously outlined, nicotinic acid emerged as an eligible candidate. Nicotinic acid has been used in the treatment of the following illnesses: pellagra psychoses (8), nicotinic acid deficiency encephalopathy (9), atypical psychotic states of senility without much evidence of pellagra (10), depressed states (11, 12), in confusional psychoses of alcoholism and drugs (13), and in cases of active psychoses without evidence of pellagra (14).



Thus, our hypothesis is that nicotinic acid will modify the LSD produced psychoses. The dosage of nicotinic acid to be used must be determined by trial and error methods. In clarifying the meaning of the word modify, we will assume that nicotinic acid could have a preventive action, that is modifying the effects of LSD when administered prior to it, and also that it could have a treatment effect, that is modifying the effects of LSD when given during the model psychotic experience.

Procedure

We selected 10 male subjects from a group of 14 volunteers. Our screening methods included a routine medical history and physical examination. Volunteers with a history of severe or recent liver damage were excluded.* A Rorschach was administered to all volunteers. Only those who were willing to participate in a related study† were included, only one of the 10 volunteers had any special knowledge of psychiatry and none reported any history of psychiatric treatment. The mean age of the group was 26 years, with a range of 19 to 31, and all were of average or above average intelligence. The group's mean years of education was 14 with a range of 10 to 18.

In order to study possible modification of LSD psychosis by nicotinic acid both from a "preventive" and "treatment" point of view, the 10 subjects were divided, at random, into 2 sub-groups of 5 members each. Sub-group A received 200 mgm. (i.v.) of nicotinic acid‡ at the height of the LSD experience. The time of the administration of nicotinic acid was not standardized since from our experience, and from the literature (16), the time at which individuals reach the height of the LSD experience varies. Sub-group B received, orally, 3 grams of nicotinic acid per day for the 3 days prior to the experimental day. Subject #5 of this sub-group also received a 200 mgm. injection (i.v.) of nicotinic acid 15 minutes after drinking the LSD. On the experimental day each volunteer received, on an empty stomach, 100 gamma of LSD.§ We decided to use this dose because our own experience shows that 80 gamma or more is needed for any sure reaction to the drug. Also, our own experience and that of Stefaniuk‖ shows that dosages of 200 gamma make it virtually impossible for the subject to give any coherent report of his experiences or for investigators to carry out any comprehensive testing programme during the experience. The decision to use a standard dosage of LSD for all subjects rather than determine dosage on the basis of body weight is based on our observations that variability of response does not appear to be particularly related to body weight.

Each subject was under constant observation by one of the investigators for at least the first 4 hours following the administration of LSD and comprehensive tape recordings were made. The experimental situation was one of relatively constant questioning and testing. On the day following the experiment each subject submitted a report of what he recalled of the experience.

RESULTS

Table I¶ summarizes the effects of nicotinic acid on LSD-produced disturbances (listed under 5 categories—proprioceptive, perceptual, etc.) for each subject of sub-group A, the group which received nicotinic acid at the height

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* It has been reported by Fischer *et al.* (15) that subjects in whom only a slight modification of hepatic function is present have a marked and prolonged reaction to LSD.

† These subjects participated in a study in which the relationship between personality structure and reaction to drugs was investigated. This study will be reported at a later date.

‡ We are using nicotinic acid as a pharmacologic agent rather than as a vitamin. It is non-toxic in much larger concentrations.

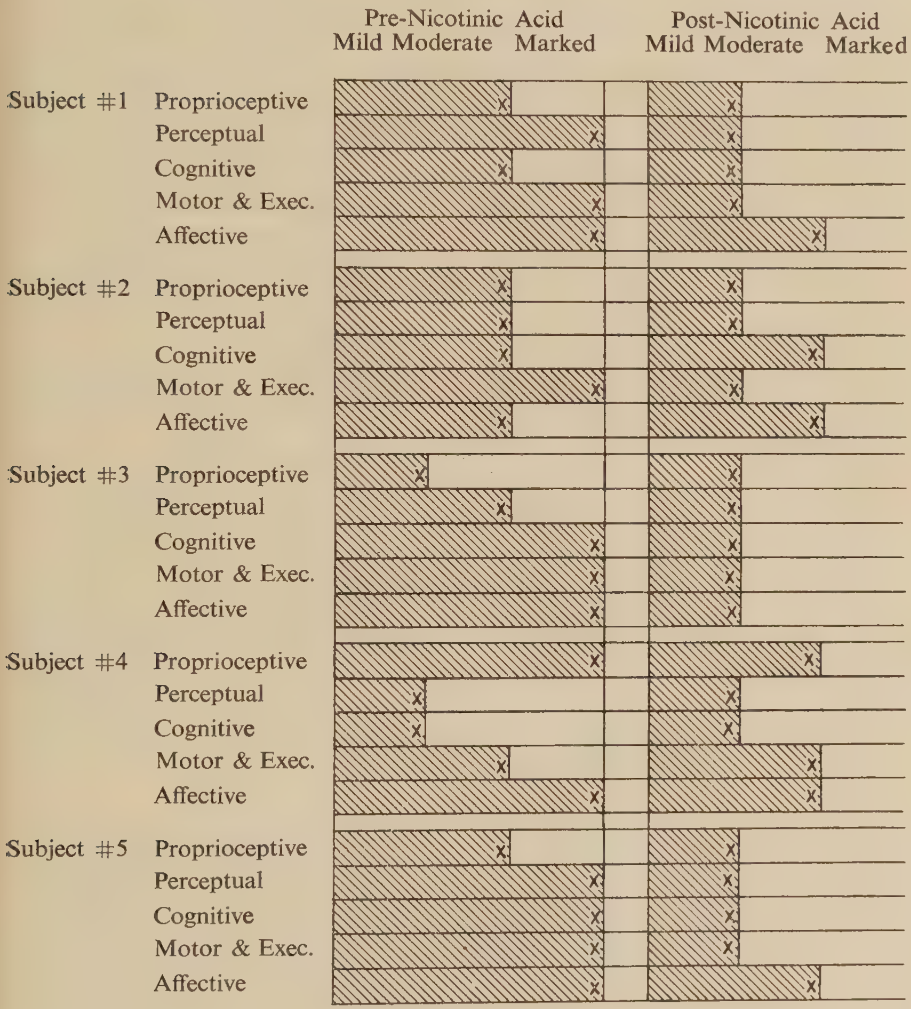
§ The LSD used in this study was provided through the courtesy of Professor E. Rothlin, Director of the Pharmacological Laboratories of Sandoz Chemical Company, Inc., Basel, Switzerland.

‖ Research Psychologist, Saskatchewan Hospital, Weyburn, Saskatchewan, carried out investigations with over 20 volunteers, each of whom received 200 gamma LSD.

¶ We realize the presentation of data in this form involves gross over-simplification. The criteria for differentiating qualitative and quantitative reactions of the kind with which we are dealing are vague. However, for those who have had little or no experience with LSD reaction in "normals" the table provides a rough guide. The only baseline we have for making the judgments we did is that established by the collective experience of members of our research unit with over 70 volunteers who received dosages of LSD ranging from 20 to 200 gamma.

TABLE I

Degree of LSD Disturbances Prior to and Following Nicotinic Acid
(Sub-Group A)



of the LSD experience. For a more detailed presentation of data on which this table is based, see Appendix A.

The variation between subjects, both as to category and degree of response to LSD, is apparent upon examining pre-nicotinic acid disturbances listed on the left half of Table I. Furthermore, the qualitative differences between subjects within any one category, for example perceptual, become clear upon examination of the left half of Appendix A. Subject #4 experienced only mild time misperception, whereas subject #5 experienced a wide-range of marked perceptual disturbances.

Table I demonstrates a clear shift of the degree of disturbance toward the left (mild) in all categories following nicotinic acid. Disturbance in the affective category, while shifting in the same direction, proved to be the most resistant to modification.

Modification in disturbances were recorded on the basis of changes which appeared within 15 minutes of the nicotinic acid injection and which were maintained at that level or decreased. If a marked reduction in disturbance was noted within 10 or 15 minutes of the nicotinic acid injection and yet 30 minutes later due to reappearance of symptoms it appeared to be only a moderate reduction of disturbance, it is recorded in Table I as a moderate disturbance under the post-nicotinic acid heading. For example, subject #4 reported a marked reduction of affective disturbances immediately following nicotinic acid, but some time later reported a return of some anxiety.

Table II summarizes the disturbances experienced by each subject of subgroup B, the group which received nicotinic acid for 3 days prior to the administration of LSD. For a more detailed presentation of the data on which this table is based, see Appendix B.

Once again reference to Table II or Appendix B points to a strong factor of inter-subject variability in response to this particular drug-combination.

Within the framework of variability there are some striking features to be noted about sub-group B results. First, difficulties in power of expression and concentration were mild compared to those found in sub-group A prior to nicotinic acid. Second, visual disturbances, which are usually the most striking feature of the LSD experience for our subjects, appeared as the major symptom in only one subject, subject #2. Finally, there were marked disturbances experienced by 3 of the 5 subjects in this series (subjects 1, 3 and 5) centering around confusion about self-identity, and unreality problems. The following are excerpts of verbatim material from the subjects:

Subject 1

"I have the feeling of trying to hang on to real things and I'm being pulled away . . . I'm localized up here and six inches to the left (points to place over his head) and it's as though I had an ear down here and an ear up there and they don't blend together . . . words seem to be very reassuring—seem to be solid, they brought me back to something that was real . . . it's as if I'm soaring around some mean little point (he was referring to the microphone which symbolized reality for him) from which I can't get free . . . This mike is my contact with reality—but this other part I feel I could almost get lost in it . . . if I break away from this (mike) I won't have to come back . . . nothing terrifying about it except the thought of losing my reference point, that would be true sensation. I feel sometimes I come right on the edge of that where I wouldn't be sensing things but rather sensations themselves . . . I see myself sitting here—stodgy kind of me and then these flights into a dimension of another world completely free of limitations I know are inherent in this world, tremendous expanded time and speed—not speed of things—just scope . . . I'm bored with real world things, ink blots and microphones . . . my experience is far more real to me than Rorschach cards . . . my experience is the real world . . . you are an individual now with a body and located in space a while ago you were merely a voice—the rest had no part." (Draws a diagram in which he depicts himself soaring around a small core of reality—at times he comes close to it and at other times he almost loses touch with it.) "This is like a conspiracy . . . you're part way

TABLE II

Degree of Disturbance when Nicotinic Acid Administered Prior to LSD
(Sub-Group B)

		Mild	Moderate	Marked
Subject #1	Proprioceptive			X
	Perceptual			X
	Cognitive			X
	Motor & Exec.			X
	Affective			X
Subject #2	Proprioceptive		X	
	Perceptual		X	
	Cognitive		X	
	Motor & Exec.		X	
	Affective			X
Subject #3	Proprioceptive		X	
	Perceptual			X
	Cognitive			X
	Motor & Exec.			X
	Affective			X
Subject #4	Proprioceptive			X
	Perceptual	X		
	Cognitive	X		
	Motor & Exec.		X	
	Affective		X	
Subject #5	Proprioceptive		X	
	Perceptual			X
	Cognitive			X
	Motor & Exec.			X
	Affective			X

in it with me . . . we're sharing a secret that those bastards in the other room don't know anything about . . . you talk about Gardner Murphy and Morton Prince, I feel that they're little spots down there—they don't really know what the hell's going on—we're on out where we've seen it—experienced it—it's tremendous their writing about something in distant words that they don't understand at all."

Subject 3

"What is the self the essential I and how does one know the I? I felt as if the 'real I' was trying hard to look after the 'drugged I' I was disturbed that there appeared to be no boundary between the two . . . the lack of control and responsibility experienced while 'drugged I' was uppermost could at any time overlap with the 'real I'. Standing by the canteen door I was aware of being different to the man behind the counter—not being able to control the difference and not particularly caring to—after all this was not a permanent state."

Subject 5

"Wait a minute—what happened . . . something happened just then. (Expt. what do you mean) . . . well now let's see the reason I came here was to take some tests and we're in the General Hospital. When you stood up and opened the door something lifts off my face—things clear up and then it's gone and Jesus you'd give anything to have it cleared up again . . . you see for a while you seemed kind of pudgy—sort of round at the edges—for a while there all of a sudden I took my glasses off—wiped my face and things seemed to clear up—you seem to just peel off the pudgyness and for a while you were clear and normal and things got smaller and I just felt relieved—for a while I seemed to come out of a dream but now I'm back in the dream. (Expt. how do you feel now) Scared—when you started to peel off you started to get real again—things were clear-cut again and now this." (This is the subject who ran down hallways in an effort to get back to reality—see Subject 5, Appendix B.)

DISCUSSION

The results will be considered under the following headings:

I. The variability of response to LSD and LSD–Nicotinic acid combinations.
II. Sub-Group A—the apparent or real antidotal action of nicotinic acid.
III. Sub-Group B—a different kind of model psychosis.

I. Variability

Since we are preparing a report of a study of the relation between personality structure and reaction to drugs in which variability is dealt with at length, we will comment here only briefly. First, the variability of response within both our sub-groups is almost as striking as the similarities perceived. Second, on the basis of the collective experience of workers in our research unit, variability of response to LSD, whether the dosage be small or large, has made it exceedingly difficult to make generalizations. Third, on the basis of the literature (1, 16, 17) most authors make reference to variability of response. However, since in the case of LSD the reactions observed are difficult to define, and space permits only limited examples in reports, it poses the problem of whether similar kinds and extent of variability are found by most investigators. A further factor adding to the complexity of the problem is that the various investigators approach the data with markedly different frames of reference which determines, to a large extent, the selection of reactions to the drug which are noted. For example, some investigators conclude that various subjects' reactions are different with respect to both quality and quantity (1), others note differences in the quality and quantity of reaction but note similar patterns of response (17), still others report essentially uniform responses on the part of their subjects (16). Thus, inter-subject and inter-investigator variability make generalizing exceedingly difficult. In this one respect at least the model psychosis resembles a naturally occurring illness called schizophrenia.

II. Antidotal Action of Niacin

The administration of nicotinic acid at the height of the LSD experience appeared to result in a striking reduction of all LSD-induced disturbances.

except affective, in all subjects but one. The reduction of the disturbances occurred within a few minutes of the nicotinic acid injection, and was maintained.

The first question that demands consideration is to what extent the modification of symptoms was due primarily to the lapse of time during which detoxication was taking place. The only adequate way to answer this question is to move the time of the administration of nicotinic acid progressively closer to the time at which LSD is taken. The effects of administering the nicotinic acid prior to LSD will be discussed in the next section. Due to individual differences and lack of criteria, it is difficult to determine the time at which volunteers taking this dosage should be expected to pass from the florid state or show definite signs of modification. On the basis of our experience, with this dosage level and using the criteria outlined by DeShon *et al.* (1), the height of the reaction lay within a period of from one to six hours after administration of the drug. This is based on a sample of only 6 subjects, none of whom passed from the florid state, as far as we could judge, prior to 3 hours and one-half, after taking the drug. DeShon *et al.* (1), using dosage levels below ours, report the height of the reaction occurring within a span of from one to five hours after administration. They do not indicate the minimum time encountered but, in the three representative cases listed, none passed from phase II (height of the reaction) prior to four and one-half hours after administration. In our subjects the nicotinic acid was injected two and one-half hours after LSD, except in one case (Subject 5) who didn't appear to enter the height of the reaction phase until two and one-half hours after administration.

A second complicating factor to be considered in attempting to assess the part played by nicotinic acid in producing the modification of LSD disturbances perceived, is the fact that ordinarily the intensity of disturbances during an LSD experience follows a wave-like rise and fall. As best we could judge, however, where modifications did appear, they were maintained.

A third question arises as to the mode of action of nicotinic acid in producing modifications of LSD disturbances. It seems clear that the action of the nicotinic acid is not that of direct biological antagonism. If it were, we should expect the modification of the LSD experience to be at least as pronounced in those subjects receiving nicotinic acid prior to the LSD which was not the case. It may be that it is acting in an indirect way, for instance, by interaction with one or more compounds produced by the introduction of LSD in the organism. It should be noted, in considering the possible mode of action, that an intravenous injection of 200 mgm. of nicotinic acid is quite unpleasant.* Therefore, apart from any specific biochemical action, it was experienced as a stressor by all subjects.

As to why the affective disturbances were more resistant to modification, no adequate explanation can be offered at this time. However, in our work with volunteer subjects it appears that certain kinds of LSD-produced disturbances are more specific and predictable than others. The proprioceptive disturbances initially experienced have been noted by all investigators and an explanation has been offered by Liddell and Weil-Malherbe (18). Perceptual disturbances, particularly time misperception and changes in size and shape of objects perceived, are common. Also, disturbances in concentration and power of expression, as well as in motor and executive functions, are noted in most subjects. It is in the spheres of affect and mood that variability appears to be the greatest. Variability in affective disturbances from our own experience, like that reported in the literature (1, 2, 16, 17, 19, 20), ranges from marked euphoria through to deep depression, from blunting through to intense anxiety. Some authors (19, 20) maintain that LSD exaggerates the previous affective state whether of a "constitutional" or temporary nature. Thus, it appears that certain reactions are more or less specific to LSD while others are more dependent upon situational and personality factors. Hyde (21) is investigating the effects of situational factors on the LSD experience and, as indicated previously, we are attempting to investigate the relationship between personality structure and LSD reaction. It is possible that nicotinic acid modifies those disturbances more or less specific to LSD but is not so effective in normalizing reactions related to the organism under general stress. For example, we have noted marked shifts in mood in some subjects when we unwittingly changed their milieu. We have been struck by the effects of leaving the subject alone for a few moments or directing our attention to a task or third person. Three of our subjects reported a marked shift in attitude toward us, we changed from friend to foe in a few seconds, or they informed us that if we were putting on an act for their benefit, it wasn't being appreciated. With respect to the possible effects of personality structure, we have some indication, for example, that subjects presenting symptoms of free floating anxiety and high blood pressure have a markedly atypical reaction to LSD.

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* One of the authors (N.A.) had the injection at the height of an LSD experience and does not feel the results are so unpleasant as to discourage the use of the dosage.

In summarizing the effects of nicotinic acid given at the height of the LSD reaction, the most obvious result is the clear-cut modification of disturbances. It seems clear that the mode of action is not that of direct biological antagonism as hypothesized initially. These results are of theoretical and practical interest with respect to the role of certain drugs in helping the organism manifesting disturbances on many levels to "normalize" (22).

III. A Different Kind of Psychosis

Within the framework of variability there appeared in the majority of Sub-group B subjects, the group that received nicotinic acid for 3 days prior to the experimental day, some uniformities of response that we have not encountered so clearly or consistently to date. First, all subjects showed much less difficulty in expressing themselves and concentrating than we have usually encountered with this dose. While it is true that in each case subjects would not shift their attention on request as readily as they did during the screening procedures, they were able to give much more coherent descriptions of their experiences for extended time periods than subjects in Sub-group A prior to nicotinic acid. In this respect one of the major difficulties we have encountered in using LSD as a "model" psychosis has been that the disturbances in expression and concentration have made it exceedingly difficult to get a coherent report of the subjects' experiences. We are not suggesting that a subject in a "model psychosis" should be able to outline his experience with textbook-like clarity. Difficulties in power of expression are to be expected when the experience to be described is different from anything previously encountered. These subjects had difficulty describing what was happening to them. Like other LSD subjects, the words, concepts and experiences in their repertoire were, for the most part, inadequate to describe the state in which they found themselves. Nevertheless, the subjects in Sub-group B did not seem to be hampered by spans of attention and concentration limited to seconds. Therefore, though their descriptions were vague, they were longer and better organized than, for example, the pre-nicotinic acid reports given by subjects in Sub-group A.

A second apparent difference in reaction on the part of this group was that the visual distortions, involving motion and change of size and shape of objects, which our subjects usually find to be the most striking feature of the LSD experience, were unusually mild in four out of five cases (subjects 1, 3, 4 and 5). Subject number two did experience the above-mentioned disturbances but, much to our surprise, proceeded to attempt to explain them, though on an over-simplified level, by working out the laws of perspective involved on numerous sheets of paper. The usual preoccupation with visual changes, like the much reduced concentration span mentioned above, has been a disconcerting factor in the LSD-produced "model psychosis". Such symptoms make it difficult to decide of what naturally-occurring psychosis it is a model.

Finally, disturbances of self-identity and reality appeared as major symptoms in three of our five subjects in Sub-group B. One subject in Sub-group A reported similar disturbances (subject #5). Stefaniuk (23), using 200 gamma dosages, found that approximately one-quarter of his subjects reported disturbances of this kind. Fischer (15) using dosages ranging from 60 to 130 gamma encountered such disturbances in less than one-quarter of the subjects. Rinkel *et al.* (2), whose subjects received from 20 to 90 gamma, found such disturbances but stated they were of minor magnitude, while Savage (4) reports depersonalization and derealization upon the administration of 20 gamma. Once again it is difficult to compare results with other investigators. The concepts involved, depersonalization and derealization, are complex and often a classification is made on the basis of a statement like "my legs feel funny" or "things look funny". We have found that the usual disturbances of concentration and expression have made it difficult for us to assign these classifications to our data except in a few cases. Thus, we were impressed by the relatively clear descriptions of these disturbances on the part of three of the five subjects in Sub-group B. It should be pointed out that vagueness, affective disturbances, and lack of co-operation when pushed were also evident in these subjects.

Several questions arise with respect to the above discussion. The sample is small. Since, as yet, we do not know what personality and situational factors are operative in accounting for the variability of response to LSD, it is conceivable that such uncontrolled factors are essentially responsible for the symptoms we attribute to the particular drug combination used. One of the five subjects (subject #4) had an unusually mild experience. Was this due to the nicotinic acid or, as we tend to feel, to personality structure factors? However, even with such limitations inherent in our results, reporting our observations appeared to be important for several reasons. The LSD psychosis has been most readily compared, to date, with schizophrenic symptoms (1, 2, 16). In making such comparisons all investigators add a note of caution with respect to obvious differences between the two. For us the unusually short spans of concentration and the more or less constant visual distortions have been primary symptoms of the LSD experience. From what little we know of the inner world of schizophrenia, this does not appear to be the case. Apart from the relatively rare hallucinations, as differentiated from illusions, and the extremely variable affective disturbances, it is in the area of depersonalization and derealization that similarity between schizophrenic conditions and the LSD experience becomes most striking. Thus, in observing three out of five cases in which depersonalization and derealization emerged with relative clarity; in which unusually short spans of concentration and more or less constant visual distortions were not major symptoms; yet in which affective disturbances, vagueness and lack of co-operation were evident, it appeared to us that here was a "model" psychosis more in keeping with the schizophrenic prototype.

If nicotinic acid was to modify the LSD reaction through direct biological antagonism, it is with this group, the one receiving nicotinic acid prior to LSD, that the most clear-cut evidence of reduced disturbance should exist. This was not the case. Fischer (24), investigating some of the factors involved in drug-produced model psychoses, postulated that compounds structurally related to LSD, and displaying higher affinity for wool-protein, should block out by competitive inhibition the LSD experience. Based on this hypothesis Fischer and Agnew (25), using the same subject, ran three experiments. In the first 80 gamma of LSD was given, in the second methylene blue followed by 80 gamma LSD, and in the third diparcol followed by LSD. Largacile, which also meets the above criteria, has also been used (26). The data to date support Fischer's hypothesis.

SUMMARY

Nicotinic acid was administered to one group of subjects at the height of the LSD experience and to another for three days prior to the administration of LSD. Tentative findings are presented which indicate that nicotinic acid, when administered at the height of the LSD experience, has a markedly normalizing effect. The lack of modification of affective disturbances is noted and discussed. The administration of nicotinic acid prior to LSD reduced disturbances in concentration and vision. However, in some subjects it produced a psychosis, the primary symptoms of which more closely resemble the primary symptoms of schizophrenia than those most commonly found when LSD alone is administered.

The mode of action of nicotinic acid does not appear to be that of direct biological antagonism as initially hypothesized.

ACKNOWLEDGMENT

The authors gratefully acknowledge the many helpful suggestions received from Drs. R. Fischer and H. Osmond.

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APPENDIX A

		LSD Symptomatology	Nicotinic Acid Symptomatology
Subject 1 24 years		12.20 100 gamma LSD (orally).	2.50 200 mgm. nicotinic acid (i.v.).
130 pounds	Proprioceptive	1.00 tense, nausea, fatigue, anorexia, shaky.	Flush, intense warmth. 3.00 no evidence of LSD symptoms.
	Perceptual	1.15–2.50 After images, rippling motion and variation of size and shape of objects; light, colour, touch and noise sensitive; size of hand changed upon suggestion.	3.02 slight "rippling" effect and sensitivity to noise.
	Cognitive	1.20–2.50 "running away" of ideas, pre-occupation, difficulty in power of concentration. Comprehension of question poor, could not organize replies.	3.04 mild difficulty in concentration, much improved grasp of questions and organization of replies.
	Executive and Motor	1.30–2.50 poor co-ordination; uncontrolled smiling; anti-social comments and unco-operative. Power of expression disturbed.	3.10 intensified effort to communicate; "I feel a much greater sense of responsibility".
	Affective	1.15 Initial euphoria followed by periodic suspiciousness.	3.50 periodic moderate suspiciousness continues. Evening: (at home) not hungry but ate supper, "felt hilarious, really enjoyed baby". "Slept well, felt like hangover next day."
Subject 2		12.10 100 gamma LSD (orally).	2.35 200 mgm. nicotinic acid (i.v.)
23 years 156 pounds	Proprioceptive	Initial dizziness and nausea. 12.40–2.35 Persistent "pressure at the back of my neck"; "cigarettes taste flat".	Flush and intense heat. 2.40 no evidence of LSD symptoms other than cigarettes continue to taste flat.
	Perceptual	12.55–2.35 Colour sensitive; objects appear "rubbery" changing shape in time with breathing; distance and time misperception; size of hand changed upon suggestion.	2.38 "The floor's stopped moving!" Some change of size and colour of objects continues—"Nothing like it was before".
	Cognitive	Confusion and some disorientation.	2.40 some confusion remains "are you quizzing me?"

		LSD Symptomatology	Nicotinic Acid Symptomatology
		2.27 "I can't get to the bottom of it", "this is an experiment isn't it?" Marked difficulty in concentration and comprehension. Replies to questions are disorganized.	Concentration improved; replies to questions much more coherently.
	Executive and Motor	1.00–2.35 Unusually talkative and aggressive in manner; resists tests—"don't feel I'm doing what I should but it's too much bother."	2.45 less talkative and more subdued; makes greater effort to report experience; still slightly aggressive. 3.20 feels LSD experience may return.
	Mood	1.10 Euphoria—persists in modified form throughout experiment.	2.57—slight tendency to smile periodically—some suspiciousness. 4.00 returns to work, feels restless—some euphoria and aggresiveness remains. Evening: ate a large supper—went for a drive, slept well.
Subject 3		9.40 100 gamma LSD (orally).	12.00 200 mgm. nicotinic acid (i.v.).
29 years 150 pounds	Proprioceptive	10.00 Initial tenseness. 10.20 Metallic taste, nausea. 10.30 hands perspiring, flush. 10.00–12.00 restlessness—anorexia.	Marked flush and heat sensation. 12.07 no sign of LSD symptoms, feels relaxed. Reports hunger. 12.30 enjoys hearty lunch.
	Perceptual	10.20 fingers feel thick. 10.30–12.00 colour, light sensitive, and objects change size and shape taking rippling motion in time with breathing. Finds certain colours very distasteful. Complains of figure-ground disturbance, time and distance and touch misperception.	12.06 no evidence of perceptual disturbances. 12.15 reports periodic return of slight motion on flat surfaces, but figure-ground disturbance no longer evident.
	Cognitive	10.30 preoccupied with Rorschach cards. 10.40 ideational perseveration. 11.00–12.00 Flow of clang, distant, loose associations and perseveration of theme, "silly" replies to questions.	12.10 pays attention to questions and gives coherent well organized replies. "I feel the way I normally do." Some tendency toward preoccupation.
	Executive and Motor	9.50 mildly aggressive. 10.30 reports difficulty in speaking. 10.45–12.00 unsteady, uncontrolled laughing, "no sense of responsibility", unable to cooperate in testing situation.	12.08 "all of a sudden I'm steady on my feet"; co-operative in answering questions and completing tests; slight tendency to smiling remains.
	Mood	10.30 mild euphoria. 11.00–12.00 marked euphoria.	12.05 euphoria markedly reduced. 1.30 returns to work—becomes preoccupied with piece of work he had been avoiding. Reports that his overcoat looked shabby and dirty. Evening: enjoyed supper; slept well.
Subject 4* 29 years 210 pounds	Proprioceptive	12.20 100 gamma LSD (orally). 12.10 (prior to LSD). Reports strong anxiety.	2.55 200 mgm. nicotinic acid (i.v.). Flush and spreading warmth.

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* This subject appeared to the examiners to have no apparent reaction to the drug—most of the material presented is based on the report of the experiences he handed in the following day.

		LSD Symptomatology	Nicotinic Acid Symptomatology
		12.30–3.00 tenseness at back of neck, anxiety becomes more and more intense. (Compares it to waiting to take off for bombing operation); shaky.	3.00 "nervousness has disappeared for first time." 3.30 "felt rather agitated and restless."
	Perceptual	2.30–2.55 time misperception.	3.05–4.00 nothing unusual noted.
	Cognitive	1.10–2.55 "couldn't follow questions which required other than stock answers; concentration impaired; "unusual slowness in thought".	3.05–4.30 "less difficulty in following and participating in conversation, still didn't feel exceptionally conversational."
	Executive and Motor	2.00–2.55 "Felt I might make ridiculous statements—so tried to discourage conversation." 2.45 Felt shaky standing, refused to walk to test steadiness.	3.05 still somewhat unsteady.
	Affective	12.10–2.55 mounting anxiety. 2.45 suspicious.	3.07 anxiety markedly reduced. "feel good for the first time." 3.40 "feel pretty tense again." 4.30 "felt relief at leaving hospital for home." 5.30 anorexia—euphoria. Enjoyed (more than usual) playing with children—pupils dilated. 7.30 noticed slight visual disturbance (rippling) for a few seconds. Had good nights sleep.
Subject 5 31 years 153 pounds	Proprioceptive	10.00 100 gamma LSD (orally). 11.30 Floating sensation and tension; nausea and neck pressure. 12.30–2.10 metallic taste, floating sensation, heightened awareness of parts of body.	2.10 mgm. nicotinic acid (i.v.). 2.15 LSD symptoms not in evidence.
	Perceptual	11.45 light and noise sensitive. 12.30–2.10 light, noise and colour sensitive; objects and person change size and shape; shifts of mood were immediately reflected in perception—warm colours, relaxed movements, soft sounds or cold colours, jerking movement, harsh noises; gross time misperception, depersonalization "Detached feeling as though I wasn't part of myself."	2.17 slight, periodic return of motion.
	Cognitive	11.00 difficulty in concentration. 12.30–2.10 preoccupation; transient and interchanging feelings of heightened reasoning capacity (actually gross oversimplification) and unreality; reporting "everything is there but it's unreal"; confused disorganized.	2.20 much less confused and reporting well organized; periodic return of mild unreality feelings.

	LSD Symptomatology	Nicotinic Acid Symptomatology
Executive and Motor	11.00 unsteadiness. 12.35–2.10 feels he can differentiate unreality feelings with effort—but disturbed over lack of control of constant mood changes which are reflected in proprioceptive and perceptual spheres, "I feel rejected, the room is cold, your face is stern and foreboding, my hands are cold." Non-co-operative.	2.20 "feel in control of myself for the first time." Co-operation much improved.
Affective	12.00–2.10 continual shifts from feelings of security, sympathy and warmth to feelings of rejection, suspiciousness and hostility.	1.50–2.45 shifts in mood greatly reduced; suspiciousness evidenced periodically. 3.15 no effects of LSD in evidence. Evening: ate a good supper and wrote rough draft of experience. 10.30 bed—slept well. Next day felt somewhat foggy mentally.

APPENDIX B

Group B. Each of the following subjects received 3 gm. of nicotinic acid (orally for 3 days preceding the experimental day

Subject 1*		12.25 100 gamma LSD (orally).
31 years	Proprioceptive	1.00 tenseness builds up, slight nausea; shaky.
155 pounds		1.30 "I feel a tremendous tenseness as though I'm waiting for something, just right on the edge of an emotional experience . . . like I'm going to blow apart."
	Perceptual	1.15 slight sensitivity to light and colour; mild touch misperception.
		1.45–4.00 marked time misperception and depersonalization; "my voice and body don't seem to belong to me, the real me is in space somewhere".
	Cognitive	1.50–4.00 marked feeling of unreality "drifting away from reality . . . experiencing different levels of reality all at once"; dissociation, hyperactive.
	Motor and Executive	1.50–4.00 rejected tests, "feel obligated to return part way to experimenter's world to report". "Your world can't begin to compete with mine."
	Mood	1.50–4.00 pleasure and excitement when not pressed to participate in testing procedures—if pressed, became hostile, . . . "like to piss on those ink blots".
		Dissociation and cognative hyperactivity continuous in modified form until approximately 2 a.m. when subject slept.
		Next day: No after effects evidenced.
Subject 2		12.35 100 gamma LSD (orally).
30 years	Proprioceptive	1.30 some tension and fatigue.
185 pounds	Perceptual	1.43 light, dark and colour sensitive.
		1.45–4.00 motion; distortion of perspective, shape, size; time and sound misperception. At one point reported "X-ray vision" (microphone did not obscure part of experimenter's arm on other side).
	Cognitive	1.55–4.15 preoccupied with visual distortions—made consistent effort with aid of drawings to explain phenomena—markedly over-simplified approach to problem.
	Motor and Executive	2.05–4.30 motor skill reduced (artist), negativistic; uncontrolled laughing; feels he is speaking with an accent (not apparent).
	Affective	1.40–4.00 Euphoria.
		4.00–4.30 insecure and suspicious.
		5.30 reluctant to go home for fear wife and family reject him in his present condition (Germanic accent).

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* Kepner reference.

		5.45 home—great feeling of relief—ate good supper, took family to band concert—bed at 11.30—slept soundly—felt fine next morning.
Subject 3 30 years		10.25 100 gamma LSD (orally).
	Proprioceptive	11.00 tense, light-headed, mild nausea.
	Perceptual	12.15–1.30 mild colour sensitivity, slight motion; enjoyed for 5 minutes illusion of 6 inches of water on floor with tiny fish swimming around. 1.15–3.30 depersonalization "real me and drugged me, which is which?"
	Cognitive	11.30 difficulty in concentration followed by preoccupation with ink blots. 1.00–3.00 feelings of unreality and spoke of different aspects of reality and unreality, of blending—"can't distinguish".
	Motor and Executive	11.00 hyperactive—restless. 11.30–1.00 uncontrolled laughing; irresponsible. 1.30–3.00 feels he is weak, dependent and inadequate.
	Affective	10.45 anxious. 11.30–1.00 Euphoria. 1.30–3.00 depression. 4.00–6.00 friend's home—philosophical, purpose of life; attempts to write about experience, can't concentrate, self-conscious, inadequate. 6.00–8.00 home—room appears dismal—philosophizing continues—slept well—some carryover next day.
Subject 4 22 years		12.03 100 gamma LSD (orally).
	Proprioceptive	12.30–2.00 extreme tension, nausea and fatigue. 2.00 vomits—tension and nausea vanish; "feel full of spunk".
	Perceptual	12.40–2.00 slight light, dark, colour and noise sensitivity. 2.00 slight motion, "reports that the ink blots look menacing".
	Cognitive	12.30–2.00 concentration difficult due to extreme nausea and fatigue.
	Motor and Executive	12.30–2.30 unsteady; poor co-ordination; restless; prior to 2.00 reluctant to participate in testing procedures—after 2.00 volunteers to do any tests we have to offer.
	Mood	12.30–2.00 anxious. 2.00–3.30 moderate euphoria. 4.00 returns to work—restlessness returns—lasts until 8.30; ate supper; retired at 10.00 and slept well. No after effects following day.
Subject 5 19 years		12.45 100 gamma LSD (orally).
	Proprioceptive	1.04 200 mgm. nicotinic acid (i.v.). 1.07 no feeling of flush or heat from niacin (he did flush). 1.25 tenseness; dizzyness; slight nausea. 2.00–4.30 periodic tenseness.
	Perceptual	1.40 "blurring sensation"; size of hands change on suggestion; "seem to be in a second story room" (basement room actually); depersonalization; "nothing's real, everything's blurry, I'm blurry". 1.50–4.15 "blurriness" in all perceptual spheres; some disorientation. 3.00 reports "everything became normal for a few seconds—then I was back in this dream world again". "Can't tell what's real."
	Cognitive	2.15–4.15 "dream world—Alice in wonderland world"; dissociation; "what I see and hear and think doesn't fit together, doesn't make sense"; loses "experimental" frame of reference for a short time.
	Motor and Executive	1.25 shaking. 2.30 asocial—anti-social tells doctor he had never seen that he was a "funny looking duck"; feels loss of control; runs down corridor to get back to "real" world.
	Affective	1.40 very mild euphoria. 2.15–4.15 shifts in mood from "dreamy relaxation", to panic and anxiety. 4.15–8.00 gradual decrease in disorientation and confusion —becomes philosophical—purpose of life—not hungry—bed at 9.00 slept well—some "blurriness" next morning—normal by noon.

A DYNAMIC THEORY OF ANXIETY AND HYSTERIA

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I

It has often been said that America and Britain are separated by a common language and a similar statement might, with equal justification, be made with respect to some of the misunderstandings between psychiatrists and psychologists. Particularly in the personality field, it is quite obvious that many of the terms used are similar, that some at least of the aims of the two groups are identical, and that methods are freely exchanged. Yet, on the whole, it cannot be said that satisfactory integration has been achieved between these two disciplines.

In principle, many practitioners in both camps would agree that as far as psychological illness is concerned the science of psychology is as fundamental to the art and practice of psychiatry as the sciences of physiology, neurology, anatomy, and so forth, are to the art and practice of physical medicine. However, like many statements of principle, such agreement would have to be qualified immediately by the statement that because of the lack of development of a well organized, empirically derived, and theoretically well founded set of principles in the field of psychology, it is at present impossible to base psychiatric procedures on this non-existent science of psychology, or to discuss the aetiology of mental disorders in terms of concepts derived from it.

Such an objection, while fairly widely held among psychiatrists, would not, in fact, give quite a fair picture of psychology as it is today. There have been very rapid strides in the last ten years or so; and in at least one fundamental part of psychology, namely, that concerned with learning theory, there has come about the beginning, at least, of a theory which might be useful in accounting for abnormal mental phenomena. This development, based as it is on the fundamental researches of Pavlov at the beginning of the century, and on the development along theoretical lines of many of his concepts by men such as Hull, Tolman, Guthrie, Spence, and many others, has now led to an impressive area of factual agreement and theoretical synthesis on many important points; there is inevitably still a great deal of argument, but as a recent survey by Osgood (1953) shows, much of this argument deals with points a good deal less fundamental than is often imagined by the protagonists. The question, therefore, arises whether an attempt should not be made at this stage to bring together in one general framework the theory of learning and the theory of personality in the hope that the dynamic laws of the former may be able to account for the derivative principles of the latter.

Two such attempts have recently been made, one by Dollard and Miller in their book *Personality and Psychotherapy* (1950), and the other by Mowrer in his book *Learning Theory and Personality Dynamics* (1950). Both are concerned in the main with the theory of neurosis, and both follow Freud in holding that neurosis in some way has its inception in the clash between the young child and those who attempt to socialize him. As Mowrer puts it, "the child has problems, needs, drives; he engages in variable, exploratory behavior, and he finds satisfying solutions. However, some of the solutions hit upon by the child will not be acceptable, or will be only temporarily acceptable, to his elders; and if the child persists in his 'immaturities', naughtiness, and 'perversity', he will be *punished*. The tacit intent of this punishment is to establish new drives—notably fears—which are specifically associated with, or conditioned to, the objectionable problem-solving behavior and thus made to compete with the underlying motivation for such behavior. Or, said more precisely, the punishment is designed to produce drives that will elicit responses which will be incompatible with the responses instigated by the original impulses or motives. In one type of situation, punishment may be designed merely to block certain types of solutions and to encourage the learning of other, socially more acceptable ones. This is likely to be true, for example, of habits of eating and elimination. In other areas, however, the punishment may be designed to block solutions to drives more or less completely, as in the case of sexuality and aggression." (1953).

Up to this point there would be considerable agreement between Mowrer and the Dollard–Miller group. However, when it comes to accounting for neurotic behaviour, there is a striking difference between their views. Dollard and Miller argue that the predisposition to neurosis is laid down whenever parents punish children so severely that they abandon overt behaviour in response to certain drives and even go as far as using their problem-solving abilities to avoid being reminded of or thinking about these drives. Normally, the resultant repressions and dissociations do not last beyond puberty; sometimes, however, the disciplinary conditioning has been so severe that it persists into later life, and as a consequence the now intensified drives of sex and aggression, while still unable to gain full expression and gratification, will intrude into consciousness sufficiently to reactivate old fears and thus produce neurotic anxiety and symptom formation. Therapy on this theory should consist of two things—on the one hand, a deconditioning and finally extinction process of the fear-anxiety combination, and on the other hand a building up, through reinforcement, of the habit of facing the drives which had been repressed and dissociated (insight acquisition).

In Freudian terms, this theory might be phrased as follows. Through parental and environmental pressure, the child develops an excessively severe *super-ego*, which in due course gains ascendance over the *ego*, which in turn is thus forced to repudiate or repress the forces of the *id*. This conflict between the too-severe powers of repression and the too-weak and unintegrated drives of the individual cause neurotic symptoms and behaviour problems. Mowrer's theory is the exact opposite of this. In his view, "neurosis arises . . . when the ego, which is initially under the *complete* sway of the id, remains essentially id-dominated and directs repressive action *against the super-ego* . . . This alternative holds that the neurotic individual is one in whom the primary drives not only have had but still have major control over the problem-solving processes and cause these to be directed toward the blocking, inhibition, or nullification of the secondary, acquired drives of guilt, obligation, and fear. The problem-solving activity which is usually referred to clinically as self-protectiveness or defensiveness thus functions in the interest of the primary drives or id, rather than, as Freud posited, in the services of the socially derived forces of the superego."

As Mowrer puts it briefly elsewhere, "it is rarely, if ever, a repression of primal impulses which initially predisposes human beings to anxiety; instead it is the socially inculcated drives of fear, gratitude, and obligation that fall under repression and which, in the act of threatening to break through and again become conscious produce anxiety". "We come to see that neurosis involves, basically, a learning deficit rather than a learning excess . . . We are also enabled to conceive the task of therapy, not as that of attempting to stay or actually reverse the process whereby the human animal is converted into a full-fledged member of his society; rather do we see therapy as the more promising venture of reinstituting and, if possible, in some measure completing the education of the laggard learner."

It would appear that the attempts of Mowrer and of Dollard and Miller to integrate learning theory and personality theory have come to grief because of the contradictions contained in their assumptions regarding personality structure. The theory espoused by one group of workers derives neurosis from the dominance of a tyrannical and over-strong super-ego, aided by the ego, over the forces of the id; the theory espoused by the other group of workers, conversely, derives neurosis from the dominance of an over-strong id, aided by the ego, over an underdeveloped and weak super-ego. In algebraic notation, Mowrer holds that $\text{Id}+\text{Ego}>\text{S.E.}$, while Dollard and Miller hold that $\text{S.E.}+\text{Ego}>\text{Id}$, where $>$ means "larger, more powerful than", or even "overpoweringly strong". This impasse has several interesting features.

In the first place, the same set of concepts taken from learning theory can apparently account with equal ease for quite antithetical theories of personality. It does not seem possible in terms of learning theory to discriminate the correct from the incorrect theory on the personality side. Learning theory does not appear to be specific enough to make divergent predictions according to divergent theories.

In the second place, the type of personality theory we are dealing with is on quite a different level from the type of learning theory built up by psychologists. The evidence it is concerned with is clinical evidence, not experimental evidence. Now clinical investigations are important in suggesting hypotheses; they cannot in themselves provide acceptable evidence for the correctness of the theories thus suggested. This widely recognized fact is particularly well illustrated by the present position as outlined above. Both protagonists claim to base their theories and their therapies on clinical observation and experience; both claim that therapeutic success in some way supports their claims. Yet these therapies are engaged in doing exactly opposite things: where Dollard and Miller advocate weakening the super-ego, Mowrer suggests strengthening it! If Mowrer were right, then patients treated according to the precepts of Dollard and Miller should actually get worse; conversely, if Dollard and Miller were right, then patients treated by Mowrer should actually get worse. In actual fact, a review of the available evidence on the effects of psychotherapy suggests that no support can be found in favour of the hypothesis that any form of psychotherapy has an ameliorating effect on neurotic disorders. Such a finding suggests that perhaps both sides claim therapeutic successes on the basis of a *post hoc ergo propter hoc* kind of argument; they have not ruled out the obvious possibility that their patients might have got better without any psychotherapy at all. Figures to show the remarkable improvement of neurotic patients not undergoing psychotherapy have been published elsewhere, and lend colour to this possibility. Indeed, a comparison of the effects of psychotherapeutic treatment led to the conclusion that "the figures fail to support the hypothesis that psychotherapy facilitates recovery from neurotic disorder" (Eysenck, 1952).

II

The great weakness of the two attempts at the integration of learning theory and personality theory which we have examined in the previous section has been the failure on the part of the authors to realize that, before a bridge can be built between the two, the alleged facts on the personality side must be established as firmly and with the same degree of experimental care and sophistication as are the facts on the side of learning theory. As long as writers are content to base their views on the personality side on nothing better than clinical insight, psychoanalytic beliefs, and evidence collected from the patient on the couch, the whole process of integration will remain purely at the semantic level and will inevitably lack any possibility of proof or disproof. The two works quoted bring out this impasse in a particularly marked manner. When Miller and Mowrer deal with issues in learning theory, they appeal to facts and perform experiments designed to prove or disprove their particular points; when it comes to personality theory, however, they immediately have recourse to pre-scientific modes of argumentation, to persuasion, and to reference to "therapies".

For the present writer, it has always seemed necessary in the investigation of personality to proceed in two stages. In the first place, what seemed to be required was an objectively established dimensional framework which could accommodate the main facts and features of behaviour relevant to mental abnormality. Experiments along these lines have been summarized in *Dimensions of Personality* (Eysenck, 1947) and in *The Scientific Study of Personality* (Eysenck, 1952), and the results have been shown to be congruent with work carried on by many other workers in the field in *The Structure of Human Personality* (Eysenck, 1953). The main findings of these various researches which are relevant to our present theory may be summarized in the following six points:

1. Human conduct is not specific, but presents a certain amount of *generality*; in other words, conduct in one situation is predictable from conduct in other situations.

2. Different degrees of generality can be discerned, giving rise to different levels of personality organization or structure. It follows that our view of personality structure must be *hierarchical.*

3. Degrees of generality can be operationally defined in terms of correlations. The lowest level of generality is defined by test-retest correlations; the next level (trait level) by intercorrelations of tests purporting to be measures of the same trait, or the same primary ability; the highest level by correlations between different traits defining second-order concepts like "g" in the cognitive field and "neuroticism" in the orectic field, or type concepts like extraversion-introversion.

4. Mental abnormality (mental deficiency, neurosis, psychosis) is not qualitatively different from normality, in the sense that a person with a broken arm, or a patient suffering from haemophilia, is different from someone not ill; different types of mental abnormality constitute the extreme ends of continuous variables which are probably orthogonal to each other.

5. It follows from the above that psychiatric diagnostic procedures are at fault in diagnosing categories, such as "hysteria" or "schizophrenia"; what is required is the determination of the main dimensions involved, and a quantitative estimate of the patient's position on each of these dimensions. (Cf. example below.)

6. The main dimensions involved in the analysis of personality for which sufficient experimental data are available to make possible a theoretical formulation are neuroticism and extraversion-introversion.

The relationship between these dimensions and current nosological psychiatric categories is well pointed out in an unpublished research by Hildebrand (1953). Proceeding on the hypothesis that the test differences between hospitalized "neurotics" and non-hospitalized "normals" (i.e. people without psychiatric involvement) would provide us with an outside criterion of "neuroticism", and that test differences between hysterics (Jung's prototype group for the concept of "extraversion") and dysthymics (patients suffering from anxiety, Jung's prototype group for the concept of "introversion") would provide us with an outside criterion of "extraversion-introversion", a battery of objective tests of persistence, suggestibility, and other traits was administered to groups of hysterics, psychopaths, depressives, obsessionals, anxiety states, mixed neurotics, and normals. Retaining the hysterics, anxiety states, and normals as criterion groups, inter-correlations were calculated between tests for the subjects in the remaining groups, and a Lawley-type factor analysis performed. Three clear-cut simple structure factors emerged, corresponding to intelligence, neuroticism, and extraversion. Intelligence tests had high loadings on the intelligence factor; the tests differentiating between the normal and neurotic groups had high loadings on the neuroticism factor; the tests differentiating between the hysterics and anxiety states had high loadings on the extraversion-introversion factor.

Factor scores on the introversion-extraversion and the neuroticism factors were then calculated for the persons in the various groups. Figure 1 gives a diagrammatic indication of the results obtained. The line separating the neurotic groups from the normal subjects was drawn so as to put 10 per cent. of the normal group on the neurotic side, this being the percentage found by R. Fraser

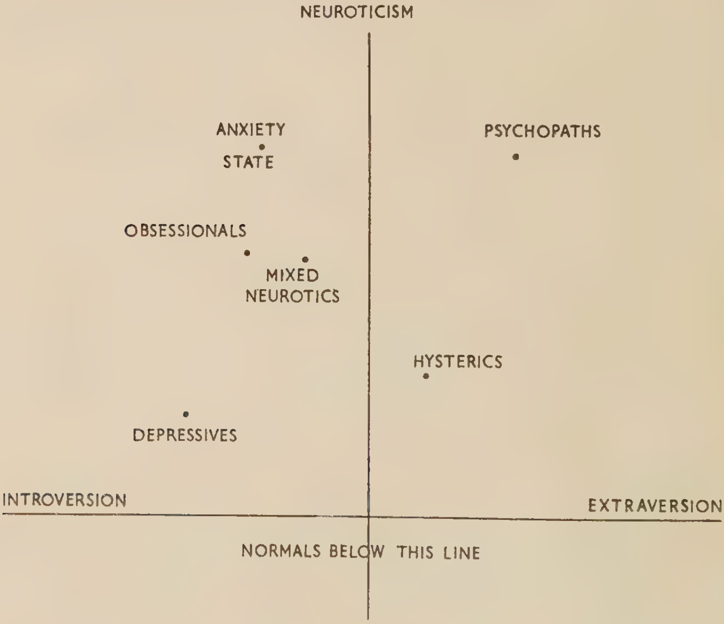

Fig. 1

(1947) to show debilitating neurotic tendencies in a normal working-class population. It will be seen that psychopaths are slightly more extraverted than hysterics, and that obsessionals and depressives are about as introverted as anxiety states. Differences between extraverted groups and introverted groups are fully significant. Mixed neurotics are intermediate between the other groups; normals are very significantly lower on "neuroticism" than any of the neurotic groups. These results allow us to use the hysteric/psychopath group on the one hand and the dysthymic group on the other as criteria for any predictions made in terms of a theory of extraversion-introversion.

So much for the first stage of investigation, which had been envisaged by us right from the beginning of this whole programme of research. However, it was also appreciated that this type of static, taxonomic, nosological, dimensional, or classificatory approach would require to be supplemented in due course by a more dynamic or causal type of investigation. If, as the author has argued, statistical factors can be regarded under certain circumstances as causal agents, then it is incumbent upon the investigator not to rest content with the extraction of statistical factors, but to go on to find the psychological or physiological causes indicated by the factor analysis (Eysenck, 1953). Consequently, in recent years our concern has been to discover the causes underlying individual differences in extraversion-introversion and in neuroticism, or, to put it in what philosophically may be a more acceptable terminology, to discover a system of relations in which the factors discovered would be the dependent variables, and certain unknown physiological or psychological properties of the nervous system would be the independent variables. In this paper, we shall be concerned almost exclusively with the dimension of extraversion-introversion; it is hoped that in due course a similar account may be possible of the causal factors underlying neuroticism. For the moment, it must be sufficient to say that we regard neuroticism as a form of drive related to the over-excitability of the autonomic nervous system, particularly the sympathetic branch. The evidence regarding the close relationship between these concepts has been discussed at some length in *The Structure of Human Personality* (Eysenck, 1953) and there is no cause to review it again here in any detail.

When we come to the construction of a theory of extraversion-introversion which, as shown in Figure 1, would also be adequate to explain the differences between the hysteric, psychopathic, criminal group on the one hand, and the anxious, depressed, obsessional group on the other, we must have in mind two objectives. In the first place, such a theory must account for the known facts. In other words, we should be able to derive or deduce these facts from our explanatory principle. In the second place, our theory should be capable of predicting facts hitherto unknown. In other words, it should enable us to verify the theory by carrying out experiments in which certain events are predicted to occur by deduction from the theory which, on other grounds, or in terms of alternative theories, would not be predictable. Such a theory will be presented in section III of this paper.

III

The theory to be presented here was adumbrated by Pavlov in his well known discussion of "experimental neurosis" (1927). Having discussed the methods by means of which so-called experimental neurosis can be produced in dogs, he goes on as follows: "It has been seen that the above-mentioned method may lead to different forms of disturbance, depending on the type of nervous system of the animal. In dogs with the more resistant nervous system it leads to a predominance of excitation; in dogs with the less resistant nervous system, to a predominance of inhibition. So far as can be judged on the basis of casual observation I believe that these two variations in the pathological disturbance of the cortical activity in animals are comparable to the two forms of neurosis in man—in the pre-Freudian terminology *neurasthenia* and *hysteria* —the first with exaggeration of the excitatory and weakness of the inhibitory process, the second with a predominance of the inhibitory and weakness of the excitatory process." This acute observation on the part of Pavlov was not developed along experimental lines by him and has been largely neglected by psychiatrists and psychologists alike. We shall formalize it in terms of a general psychological law proposed by Hull, namely his law of *reactive inhibition*.* This law reads as follows: "Whenever any reaction is evoked in an organism, there is left a condition or state which acts as a primary negative motivation in that it has an innate capacity to produce a cessation of the activities which produce the state" (1943). Hull expands this statement as follows: "All responses leave behind in the physical structure involved in the evocation, a state or substance which acts directly to inhibit the evocation of the activity in question. The hypothetical inhibitory condition or substance is observable only through its effect upon positive reaction potentials. This negative action is called *reactive inhibition*. An increment of reactive inhibition (ΔI_R) is assumed to be generated by every repetition of the response (R), whether reinforced or not, and these increments are assumed to accumulate except as they spontaneously disintegrate with the passage of time."

It is easy to see what Pavlov and Hull had in mind in advocating this concept of inhibition. Whenever a stimulus-response connection is made in the central nervous system there are created both excitatory and inhibitory potentials. The algebraic sum of these potentials determines the amount of learning that takes place, and through it the particular reaction the organism makes whenever the stimulus in question is presented again.

Excitatory and inhibitory potentials have ascertainable properties which are in many ways different from each other. To take but one example, inhibitory potentials dissipate more quickly in time than do excitatory potentials. It has been found quite impossible to account for the observed effects of conditioning and learning in terms only of excitatory potential; the effects of extinction and recovery, of disinhibition, of inhibition with reinforcement, and of conditioned inhibition in the Pavlovian system, and the effects of reminiscence, massed versus spaced learning, serial learning position effects and so forth, in the Hullian learning system equally point to the absolute necessity of some such concept as expressed in Hull's law of inhibition quoted above. There is no space here to quote the evidence in any detail, and the interested reader must be referred to the excellent summary given by Osgood (1953).

Having taken Hull's law of inhibition as our point of departure, we must next propose what may be called *a postulate of individual differences: Human beings differ with respect to the speed with which reactive inhibition is produced,*

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* While this law is usually associated with Hull and is therefore quoted in the form which he has given it, it should be noted that a very similar law was proposed by Spearman in 1927. This, his so-called law of *fatigue*, reads as follows: "The occurrence of any cognitive event produces a tendency opposed to its occurrence afterwards." Spearman does not remark on the similarity of his law to Pavlov's conclusions and Hull does not quote Spearman in connection with his own formulation. It would be interesting to know the views of these authors on the relevance of the work of their colleagues, but unfortunately they seem to have been too preoccupied with building up their own systems to pay much attention to evidence collected outside.

the strength of the reactive inhibition produced, and the speed with which reactive inhibition is dissipated. These differences themselves are properties of the physical structures involved in the evocation of responses." This postulate is implicit in Pavlov's account but has been curiously neglected by Hull, who hardly ever deals with individual differences of this kind.

To make our theory complete, we must add one further postulate which may be stated as follows: *Individuals in whom reactive inhibition is generated quickly, in whom strong reactive inhibitions are generated, and in whom reactive inhibition is dissipated slowly are thereby predisposed to develop extraverted patterns of behaviour and to develop hysterico-psychopathic disorders in cases of neurotic breakdown; conversely, individuals in whom reactive inhibition has developed slowly, in whom weak reactive inhibitions are generated, and in whom reactive inhibition is dissipated quickly, are thereby predisposed to develop introverted patterns of behaviour and to develop dysthymic disorders in cases of neurotic breakdown.*" These two postulates, added to the law of reactive inhibition, are, it is suggested, sufficient to account for the observed facts on which the dimension of extraversion-introversion is based, and enable us to make predictions which are experimentally verifiable. We shall deal with the second of these points first, in section IV, and then, in section V, undertake to show how known facts can be accounted for in these terms.

IV

The first prediction, made on the basis of our theory, relates to the establishment of conditioned responses. It follows directly from the Pavlov-Hull theory that with individuals in whom the excitation-inhibition balance is tilted in the direction of strong excitation and weak inhibition, conditioned responses should be formed quickly and easily and should be difficult to extinguish. Conversely, in individuals in whom the excitation-inhibition balance is tilted in the direction of weak excitation and strong inhibition, conditioned responses should be formed slowly and with difficulty and should be easy to extinguish. No work along these lines appears to have been done in Pavlov's laboratory, but some corroborative evidence has been produced by several workers. Unfortunately, most of this work has consisted merely in relating anxiety as a symptom to conditionability. This is in line with our hypothesis in view of the fact that symptoms of anxiety, as shown in Figure 1, are located on the dysthymic-introverted side of our dimension. However, the proof is far from complete as symptoms of anxiety also show projections on to the dimension of neuroticism, so that it might be possible to account for the conjunction between anxiety and conditionability in terms of neuroticism rather than in terms of extraversion-introversion. Such an attempt has indeed been made by Taylor (1951) and Spence and Taylor (1951) who, working on University students, showed that eye-wink conditioning occurred more quickly and more easily in students who, according to questionnaire responses, showed evidence of anxiety as compared with students who failed to show such evidence.

Making use of Hull's formula ${}_{S}E_{R} = {}_{S}H_{R} \times D$, where ${}_{S}E_{R}$ represents excitatory potential, ${}_{S}H_{R}$ habit strength, and D drive strength, they argue that anxiety is related to drive level, and that consequently higher status of anxiety should lead to quicker conditioning (${}_{S}E_{R}$) because of increases in drive strength (D). Their experiments do not provide crucial evidence with respect to the two theories involved (their own and the one outlined in section III) as the same prediction would be made in terms of both hypotheses. The same ambiguity is found in the work of Bitterman and Holtzman (1952), of Welsh and Kubis (1947) and of others who have carried out experimentation in this field. In every case the concern of the experimenters has been with the relationship between dysthymic personality and conditionability, and in every case it is possible to account for the greater conditionability of the dysthymic in terms of his *introversion* or in terms of his *neuroticism.*

The crucial experiment, therefore, requires the examination of three groups, namely, a group of dysthymics, a group of normals, and a group of hysterics. If the easy conditionability of the dysthymics is related to their neuroticism, then hysterics also should be easily conditionable and the normals should be less conditionable than both neurotic groups. If, on the other hand, the easy conditionability of the dysthymics is related to introversion then it would follow that the hysterics should be the least conditionable group, with the normals (who, being selected on a chance basis, should be on the average neither introverted nor extraverted) in between the two neurotic groups.

This crucial experiment was carried out in this laboratory by Dr. C. Franks (1954). Using the eye-wink to a puff of air as the response, and a tone as the conditioned stimulus, he plotted the acquisition and the extinction of the conditioned response to the tone in eighteen conditioning and ten extinction trials for groups of dysthymics, normals, and hysterics, respectively. The main results of his study are shown in Figure 2 where it will be seen that, as predicted in terms of our theory, the dysthymics condition more quickly, condition more strongly, and extinguish less quickly than do the normals, while hysterics condition less quickly, condition less strongly, and extinguish more easily than do the normals.

These results suggest very strongly that conditionability is related to extraversion-introversion and not in any way to neuroticism. We thus find that our first prediction is borne out by the facts (Dr. Franks also used P.G.R.

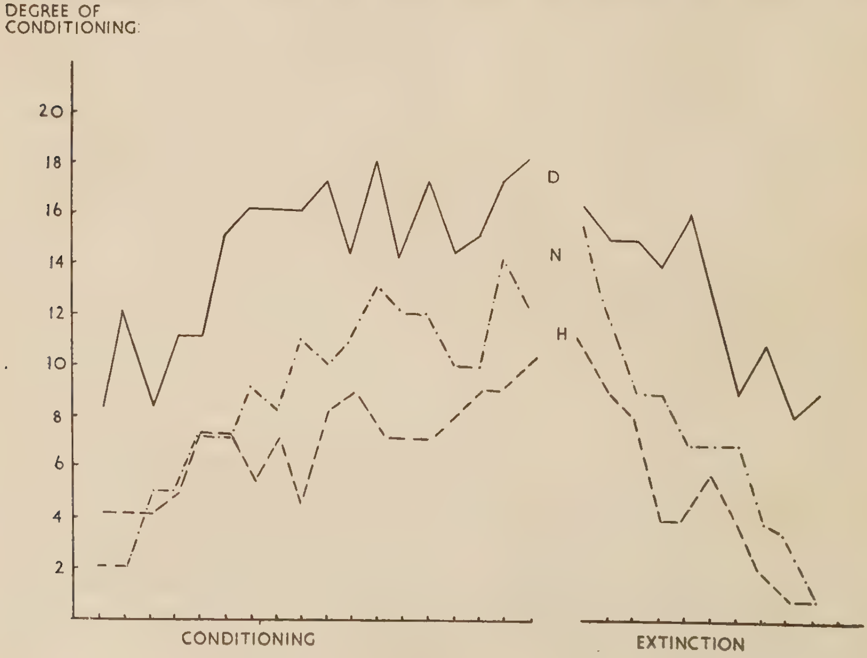

FIG. 2

conditioning and found similar results there. There is no space here, however, for going further into his well designed and carefully controlled experiment.)*

It would be erroneous to think that the law of inhibition, which was quoted earlier in this paper, is restricted entirely to the phenomena of learning and conditioning. Pavlov is often misrepresented as having considered his conditioning procedure as a paradigm for learning. This interpretation and the developments stemming from it is almost entirely due to American learning theorists. In actual fact, Pavlov was far more interested in using the conditioning procedure to establish the laws of cortical functioning; these laws he considered would be of universal applicability and would account, he thought, just as much for perceptual phenomena as for those of learning.

Consequently, it appeared desirable to attempt a proof of our general hypothesis in a field not directly connected with learning and conditioning, and accordingly a search was made for phenomena in the perceptual field which would lend themselves to a crucial experiment. The particular phenomenon decided on was the so-called figural after-effect, discovered by Gibson (1933) and by Köhler and Wallach (1944). In essence, the phenomena studied by these writers showed beyond doubt that constant stimulation of parts of certain sensory surfaces, such as the retina, sets up states of inhibition in corresponding areas in the cortex which have measurable effects on the perception of stimuli later presented in the same region. As an example, consider Figure 3. In the first part of the experiment, the subject is instructed to fixate a small cross to the left of which is a circle, as shown in 3a. After five minutes of constant stimulation of part of the retina by this circle the stimulus is withdrawn and two squares, separated by a fixation point, as in 3b, are substituted.

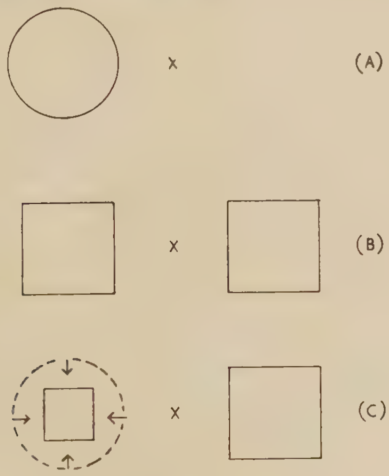

Fig. 3

According to Köhler's theory the inhibitory after-effects produced by the inspection of the circle originally presented (Köhler calls these "satiation effects") should lead to a displacement of the contours of the square now seen in the same part of the retina as the circle was originally, away from the contour of that circle. This effect is illustrated in Figure 3c and it will be seen that the observable effect would be a displacement of the sides of the left square, and consequently a shrinkage in size of this square as compared with that on the right side. Thus, inhibition or satiation effects produced by inspection of the circle would show themselves in displacement or shrinkage effects of a figure presented in the same part of the visual field. These theoretical effects are actually observable, are of considerable size, and show marked individual differences.

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* Group averages do not tell us much about the adequacy of a test for differentiating different groups. Eye-wink conditioning alone was found to differentiate hysterics from dysthymics with a classification error of only 12 per cent.; a combination of eye-wink and P.G.R. conditioning, using a pre-arranged weighting system, i.e. not capitalizing on chance errors, separated out the two groups with no misclassification whatsoever.

Now effects of this kind appear to be very much in line with the law of inhibition, as quoted above, and are indeed predictable from it. Köhler's notion of "satiation" appears to correspond exactly to the Pavlov–Hull notion of "inhibition". It is interesting to note that in this molar law of satiation-inhibition the arch-Atomist Pavlov and the arch-Gestaltist Köhler appear to have arrived at identical concepts or laws. There is, indeed, a further similarity between these two workers. Both attempt to account for their molar principles in terms of molecular (physiological) principles which, because of their unorthodox nature, have not found ready acceptance among physiologists and neurologists. It should perhaps be pointed out, therefore, that in accepting the reality of the phenomena of inhibition and of satiation, which can hardly be gainsaid, we do not wish to imply acceptance of the physiological theories associated with Pavlov and Köhler respectively. Konorski (1948) has discussed the relationship between Pavlov's physiological and neurological theories and those of Sherrington and other orthodox physiologists in some detail, and Osgood (1953) has attempted to do a similar service for Köhler's figural after-effects. While these theoretical contributions are interesting and important, they are not strictly relevant to a psychological theory of the kind developed here, which remains throughout at the molar level and is not concerned with physiological details.

If we agree, then, to accept the hypothesis that satiation effects of the kind described are the product of reactive inhibition as defined, then it follows immediately from our postulates that figural after-effects should appear earlier among extraverts, they should appear more strongly in extraverts, and they should disappear more slowly in extraverts as compared with introverts. If we take hysterics as a prototype of our extraverted group and dysthymics as a prototype of our introverted group, then clearly these predictions admit of an easy disproof. An experiment along these lines has been reported by the writer elsewhere (1954).

The test used for this purpose was the kinaesthetic figural after-effect measure, originally described by Köhler and Dinnerstein (1947), and adapted by Klein and Krech (1952), whose procedure was followed. Figure 4 shows the test in detail. The apparatus consists of a comparison scale, marked A, a stand, marked B, a test object, marked C, and a stimulus object, marked D. These are all made of wood and movable riders are affixed to all three objects in such a way that the position of thumb and forefinger is kept constant as the subject moves these two fingers up and down along the sides of the objects. The apparatus is so arranged as to present the comparison scale to the left of the seated subject, and either the test or stimulus object to his right. The task of the subject is to adjust the position of the rider on the comparison scale in such a way that the width of the wood between his two fingers is subjectively equal to the width of the wood between the fingers of his right hand, i.e. to arrive at a point of subjective equality between the width of the test object and the width of the comparison scale. Having determined this subjective equality, the experimenter then instructs the subject to put the fingers of his right hand into the rider of the stimulus object, which is somewhat broader than the test object (2½ inches as compared with 1½ inches), and to stroke the sides of the stimulus object for varying periods of time (those employed in this experiment were periods of 30, 60, 90, and 120 seconds). After this process of constant stimulation, which corresponds to the inspection of the circle in the visual experiment described before, the subject goes back to the test object and again establishes a point of subjective equality. The prediction is that there should be a shrinkage of the test object corresponding in principle to the shrinkage of the square shown in Figure 3 as a result of the constant stimulation produced by the stimulus object. Thus, our prediction would be that hysterics should show a greater degree of shrinkage than would dysthymics.

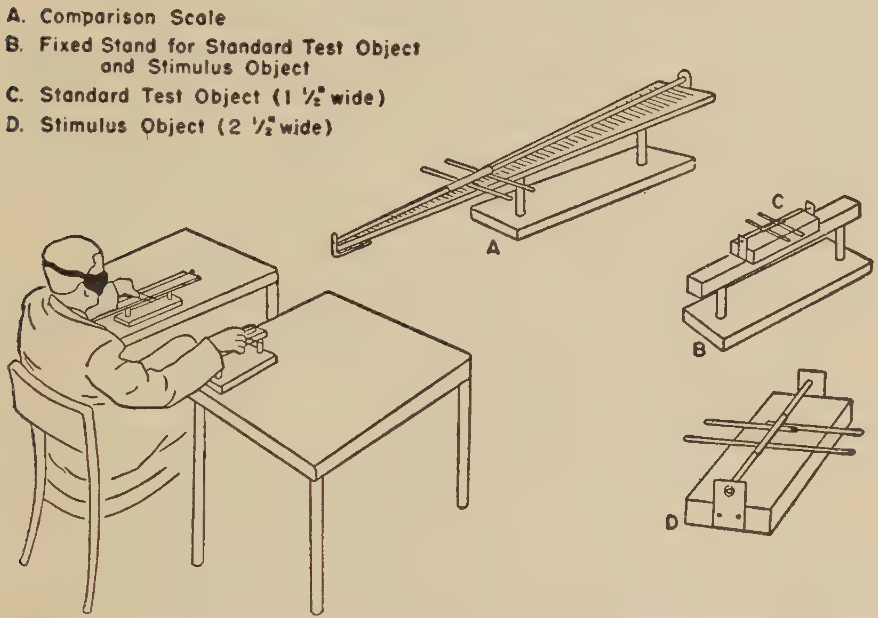
A. Comparison Scale
B. Fixed Stand for Standard Test Object and Stimulus Object
C. Standard Test Object (1 ½" wide)
D. Stimulus Object (2 ½" wide)
A
C
B
D

FIG. 4.—Diagram of kinesthetic figural after-effect test.

Results of such an experiment are given in Figure 5. The ordinate depicts the amount of decrement, the abcissa shows the various rubbing periods. Also shown on the abcissa are determinations made after rest periods of five and a further ten minutes respectively. It will be seen that our prediction is borne out at a statistically significant level in every detail.

Hysterics develop satiation effects more quickly, they develop them more strongly, and the effects persist longer. Thus, it will be noticed that even after a rest period of 15 minutes hysterics still show satiation effects which are stronger than those shown by dysthymics immediately after a stimulation period of 120 seconds. These results are very encouraging and suggest that our hypothesis may not be altogether erroneous in its main assertions. The results are particularly important because they are predicated on the correctness of two independent hypotheses, (1) that extraverts show more cortical inhibition than introverts, (2) that the laws of satiation in the perceptual field are formally identical with the laws of inhibition in the learning field.

The experiments described in this section were carried out especially in order to provide evidence regarding the power of our theory to make possible testable deductions. Large numbers of other deductions could, of course, be made in terms of the phenomena of learning and perception respectively which are associated in the literature with the concepts of inhibition and satiation. Thus, it would seem to follow from our hypothesis that reminiscence effects should be stronger in hysterics, that serial learning position effects should be more marked, and that superiority of spaced over mass learning should be far more clearly marked in hysterics than in dysthymics. On the perceptual side, the "extinction" effects noted by Bender (1951) should be more strongly marked in hysterics, thresholds for apparent movement phenomena should be shifted further for hysterics than for dysthymics by constant stimulation, and the increase in the length of after-images as a function of the length of exposure of the original stimulus should be less marked in hysterics than in dysthymics. There is little point in adding further predictions; anyone familiar with the literature will be able to make his own deductions from the principles enunciated in the previous section.

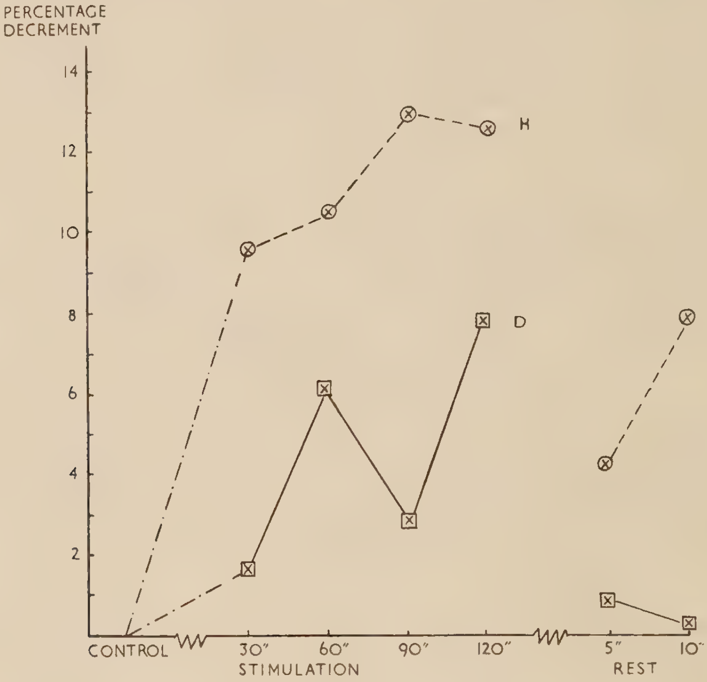

FIG. 5

V

We must now make an attempt to account for the known facts relating to extraversion and introversion in terms of our general hypothesis. In doing so we shall make use of the concept of *socialization*. By this term we shall understand the process by means of which the values and standards of the society in which a person lives are inculcated into that person. In our society this process of socialization is concerned particularly with the development of certain accepted rules regarding the suppression of overt aggressive and sexual impulses.

The process of socialization, i.e. the acquisition by the individual of a certain set of standards of conduct and behaviour prescribed by society (in different terminology, the acquisition of a conscience or of a super-ego), is considered to be mediated by a process of conditioning. In evaluating such a statement we must bear in mind a distinction drawn by many theorists between *learning* and *conditioning*. This distinction was originally proposed by Konorski (1948), in Pavlov's laboratory, who labelled the phenomena covered by these two terms conditioning of the first type and conditioning of the second type. Skinner's differentiation between S-type conditioning and R-type conditioning emphasizes a similar differentiation (1938). The distinction made by Hilgard and Marquis (1940) between classical and instrumental conditioning also refers to the same facts. Probably the clearest account, however, is that given by Mowrer (1950) in his advocacy of "the dual nature of learning". In what follows we shall make use of his account without necessarily endorsing the totality of his system.

In this account, Mowrer starts by pointing out that in all mammals the individual organism is divided into two great response systems, that of the *skeletal muscles* and that of the *smooth muscles* and *glands*. The responses mediated by the latter he calls *physiological*; those mediated by the former he calls *behavioural*. This fundamental dichotomy he links with the fact that mammals have not one nervous system but two. "Responses of the skeletal muscles are mediated by the *central nervous system*, whereas responses of the visceral and vascular parts of the organism are mediated by the *autonomic nervous system*. In terms of structure and organization, as well as mode of functioning, these two nervous systems are radically different; and it is by no means unreasonable to suppose that the responses which they mediate are subject to very different learning processes. As a further parallel to this basic dichotomy we may note the familiar differentiation between *voluntary* and *involuntary* responses. Without exception, the visceral and vascular responses are beyond direct voluntary control, whereas all of the skeletal responses . . . are or may be brought under voluntary control."

Normally, visceral and vascular responses subserve homoeostatic functions. They may, however, be made to occur not only in response to actual physiological needs but also in response to conditioned stimuli of various kinds. When autonomic responses occur on this latter basis, as anticipatory states, they produce rather than eliminate physiological disequilibrium and are consciously experienced as emotion. "As such, they play enormously important motivational roles, roles so important to the survival of the organism that it is easily understood why the learning of these responses should be automatic, involuntary, distinct from the type of learning whereby ordinary habits are acquired. Biologically, it is clearly necessary that living organisms be equipped with a nervous system which will cause to be fixated those skeletal responses which reduce drives and give pleasure. But it is equally evident that living organisms must also be equipped with another nervous system which will cause emotional responses to be learned, not because they solve problems or give pleasure in any immediate sense, but because without such responses the organism would have slight chance of survival. There are grounds for believing that all emotions (including fear, anger, and the appetites) are basically painful (i.e. all have drive quality); and it is hard to see how they could be acquired by the same mechanism which fixes those responses (of the skeletal musculature) which are problem solving, drive reducing, pleasure giving. The latter are learned when a problem is resolved, ended; whereas it is often necessary that emotional responses become conditioned to signals which are associated with the *onset*, not the termination, of a problem."

This distinction between conditioning mediated by the autonomic nervous system and learning mediated by the central nervous system is likened by Mowrer to the difference between Freud's *pleasure principle*, which would correspond to learning, and the *reality principle*, which would correspond to conditioning. "In other words, living organisms acquire conditioned responses, or emotions, not because it is pleasant to do so, but because it is *realistic*. It is certainly not pleasant to be afraid, for example, but it is often very helpful, from the standpoint of personal survival."

Lastly, Mowrer goes on to link the distinction between conditioning and learning with that between *training* and *teaching*. He points out that the acquisition of new responses by an individual comprises two different kinds of response. In the first place, there are those responses which are intrinsically rewarding and which help the individual to solve problems which without teaching he would have had difficulties in solving for himself. There are also responses, however, which the individual has to learn, not because they are useful to him in any direct sort of way but because these responses are required by society. "By and large, the solutions to individual problems involve the central nervous system and the skeletal musculature, whereas the solutions to social problems involve the autonomic nervous system and the organs which mediate emotional responses. Intrinsically, it is hardly helpful to the individual to be told, 'Thou shalt not do thus and so', but it may be socially very necessary, and, in the long run but not in any immediately discernible psychological sense, also advantageous to the individual."

This acquisition of socially useful responses is equivalent to our concept of *socialization* and is called *training* by Mowrer. "Teaching may be defined as the process whereby one individual helps another learn to solve a problem more quickly or effectively than would be likely on the basis of that individual's own unaided, trial-and-error efforts. Here we are dealing with 'items of culture' which are individually helpful. Training, by contrast, may be thought of as involving learning whose primary objective is social rather than individual. In this connection one naturally thinks of 'items of culture' which are associated with such words as 'morality', 'character', 'social responsibility', etc."

We cannot go further into Mowrer's account of the process of socialization as mediated by a process of conditioning; the reader who wishes to assess the evidence on this point for himself must be referred to the original publication. Instead, we must now trace the consequences which follow from this theory with respect to the personality patterns of extraverts and introverts respectively. It will be clear that if the process of socialization is based on a conditioning procedure, then, other things being equal, the extreme introvert, subjected to a standard process of cultural indoctrination, should become over-socialized as compared with the average sort of person, while the extreme extravert, subjected to the same process, would become under-socialized as compared with the average person. We shall consider in a moment what happens when other things are not equal; for the time being, let us consider whether in fact the hypothesized consequences can be observed.

The facts seem to fit the pattern remarkably well. It is one of the characteristics of the psychopathic, hysterical group that they transgress the morals of society in many ways (lying, stealing, sexual delinquency, avoidance of responsibility, etc.), while dysthymics, on the other hand, are over-scrupulous, over-concerned with ethical and similar problems, and as over-inhibited in the behavioural field as the hysterical, psychopathic group is under-inhibited.* This clinical pattern is apparent even in children and is shown very strongly marked in Figure 13 in *The Structure of Human Personality* (Eysenck, 1953), where the extraverted group of symptoms, as derived from Ackerson's study of *Children's Behavior Problems* (1942) includes such notations as fighting, swearing, lying, stealing, truant, violent, rude, destructive, disobedient, and egocentric, while the introverted group includes such notations as sensitive, absent-minded, day-dreams, depressed, seclusive, inefficient, and so forth.

On the experimental level we again find that many of the facts can be accounted for in these terms. The excessively high level of aspiration of the dysthymics as compared with the excessively low level of aspiration of the hysterics appears to be a direct consequence of over- and under-socialization respectively (Eysenck and Himmelweit, 1946; Miller, 1951). The preference of hysterics for sex humour as compared with the preference of dysthymics for cognitive humour also follows directly from the hypothesis (Eysenck, 1947). The disregard for rules shown by criminals, psychopaths, and hysterics on the Porteus Mazes Test when infringements of rules against cutting corners, lifting pencils, etc. are scored independently of intelligence, again show the lack of socialization of the extraverted group (Hildebrand, 1953; Porteus, 1945; Foulds, 1951). On tests measuring propensity towards cheating, Biesheuvel (1953) has found psychopaths obtaining much higher scores than other groups. The failure of extraverts to develop a vocabulary equivalent to their abstract intelligence; the tendency to lay stress on speed rather than accuracy in their work; the lack of the socially valued quality of persistence (Eysenck, 1947)—these and many other facts established in experimental work are all directly deducible from the hypothesis of under-socialization of extraverts and over-socialization of introverts, respectively.

Of particular interest in this connection is a study of social attitudes recently published by the writer (1954). From our hypothesis we would deduce that the attitudes of extraverts and introverts would differ sharply with respect to a variety of aggressive and sexual practices. When this hypothesis was put to the test it was borne out at a very high level of significance indeed. While the picture was somewhat complicated by the inescapable conservative-radical dichotomy, it nevertheless provided strong support for our hypothesis. Extraverts who, politically, were situated to the left of centre particularly frequently endorsed attitudes favourable towards a less restricted and less inhibited sex life. Thus, they were in favour of relaxing divorce laws, abolishing abortion laws, legalizing companionate marriage, abolishing licensing laws, and so forth. Extraverts to the right of centre, politically, were characterized by attitudes having a strongly aggressive cast. They tended to favour war, flogging of sex criminals, the death penalty, and the harsh treatment of transgressors generally. Compared with these extraverted beliefs introverts strongly supported the main social restraints against aggressive and sexual tendencies, i.e. religious and ethical beliefs and practices. These results fit in too well with our hypothesis to be accountable for in terms of chance.

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* It is unfortunate that the term "inhibition" is commonly used in so many different senses. As far as the usual physiological meaning of the term is concerned, as discussed, for instance, by Eccles (1953), little confusion is likely to arise. Experience has shown, however, that some confusion is caused by the fact that cortical inhibition as conceived here is considered to be a causal agent of *lack* of behavioural inhibition, whereas lack of cortical inhibition, on the other hand, is accompanied by inhibited behaviour. This semantic difficulty needs only to be pointed out in order to become innocuous.

So far, we have assumed that the environmental influences which society brings to bear on the growing child in order to make him socially acceptable are roughly equal for all the people concerned. This is almost certainly not true and what we are dealing with in the grown-up person is obviously a balance of the socializing influences society has exerted on him and the innate receptivity (conditionability) of the individual towards these influences. Proof of this proposition has been given again in connection with social attitudes, and the main outcome may briefly be quoted here.

We have noted above a set of beliefs held by extraverts of radical or conservative views respectively. Taking all these attitudes together and contrasting them with those held by right and left wing introverts, we arrived at a distinction between tough-minded (extraverted) and tender-minded (introverted) beliefs. By carefully balancing right and left wing attitudes, a measuring scale for tough-mindedness was finally produced which was quite independent of radicalism-conservatism, and which correlated with extraversion. Using this scale and basing ourselves on the theory developed above, the prediction was made that middle-class groups would be less tough-minded than working-class groups. The grounds for making this prediction were as follows. There is no reason to expect that any differences exist between classes with respect to conditionability. It is known, however, from the work of Allison Davis (1944) and his colleagues in the United States, and of Himmelweit and her colleagues in this country (1953) that middle-class children on the average are exposed to a stronger and more definite socialization process, particularly with respect to the control of aggressive and sexual impulses. (The work of Kinsey is also relevant here (1948, 1953).) In terms of our theory the impingement of a strong and a weak socialization process respectively on groups not differentiated with respect to conditionability should lead to differential attitudes and behaviour, and this prediction was, in fact, borne out among all the groups studied and at a very high level of significance.

Another study along rather different lines, making the same point, is that of Hewitt and Jenkins (1946), quoted in some detail in *The Structure of Human Personality* (Eysenck, 1953). They showed that over-inhibited behaviour in children was found in conjunction with repressive attitude on the part of the parents, while aggression and delinquency in children were found linked with attitudes of parental rejection and negligence. The correlations are in the neighbourhood of ·6 and the findings certainly are such as would have been predicted in terms of our theory, i.e. the more strongly socializing the pattern of discipline, the more introverted the behaviour pattern of the child, and the less socializing the pattern of discipline, the less introverted the behaviour pattern of the child. (The proof furnished by this study is not absolute, of course, because hereditary influences are not taken into account. A more complex study along similar lines would be required to weigh the respective influence of these two factors.)

We have only been able to touch on a few points where the theory outlined above enables us to account for the observed facts; a full discussion of the whole evidence must await a later and more extensive publication. Before closing this section, however, we would like to draw attention to the fact that this account also succeeds in reconciling the contradictory views of Mowrer (1953) and Miller and Dollard (1950) quoted in our first section. If we can equate the concept of socialization with that of super-ego, as used by these writers, then it becomes clear that Mowrer identifies the neurotic entirely with the hysteric, psychopathic type of person, while Miller and Dollard are concerned entirely with the dysthymic group. The under-socialized extraverted neurotic is described very well in Mowrer's formula: $Id+Ego>S.E.$, while the over-socialized introverted neurotic is described equally well in Miller and Dollard's formula: $S.E.+Ego>Id$. Ironically enough, then, it turns out that the theories of these men, while ostensibly concerned with neurosis as such, are really relevant to the extraversion-introversion dichotomy. This illustrates particularly well the importance which attaches to a thorough taxonomic or dimensional analysis of the field before an attempt is made to go beyond this to the dynamic or causal type of analysis.

VI

The present section is devoted to an extension of the theory outlined above to the field of brain damage. There appears to be little doubt that clinically the pattern of symptoms of the hysteric often shows considerable similarities to the pattern of symptoms of the brain injured person. This casual observation would seem to lend some support to a hypothesis which was never formally stated by Pavlov but which can be derived from his writings and those of other experimentalists in this field, namely, that brain damage in general results in an increase of inhibitory potential as compared with the pre-injury phase. This theory received strong experimental backing from the work of A. Petrie (1952), which has been outstanding in this field. Making use of objective tests which were known to be measures of the extraversion-introversion dimension, and applying these to leucotomy cases before and after their operation, she showed that on each of the tests there was a marked shift in the direction of greater extraversion. This shift is exactly in line with the hypothesis that brain injury (in this case surgical interference) produces an increase in inhibition, and consequently an increase in extraversion, which is measurable in terms of the objective tests used. The findings, which have since been duplicated in several countries, provide a firm support for this theory.

Further support comes in terms of the two tests of inhibition which we mentioned in section III, namely, those of conditioning and figural after-effect. If brain injury produces an increase in inhibition, then we should expect brain injured persons to be less easily conditionable than comparable groups of non-brain injured persons. Reese and his associates (1953) have recently shown that this is indeed so, and that lack of conditionability is a direct consequence of brain damage.

In the field of figural after-effects our prediction would, of course, be that the brain injured would show greater figural after-effects than the non-brain injured. This prediction has been verified by Klein and Krech (1952) who, using the same apparatus illustrated in Figure 4, obtained the results given below in Figure 6. It will be seen that their brain-injured group showed reactions very similar to our hysterical group, while their normal group showed reactions intermediate between our hysteric and our dysthymic groups. These results also agreed very well with our prediction.

Another strand of evidence which should not be overlooked is the work of Bender, as summarized, for instance, in his book *Disorders in Perception* (1951). He makes use of the concept of extinction, which appears to be closely related to the concepts of inhibition and satiation. His method essentially consists of touching the face and the hand of his subjects simultaneously while the latter's eyes are closed. In brain damaged patients a considerable amount of extinction is found, i.e. the patient reports only the facial touch and not that on the hand. With normal people this phenomenon is decidedly rare. Of particular interest in this connection is Bender's observation that "extinction on one half side of the body may be found in patients with psychoneurosis who show hysterical features, but in these cases the sensory changes do not conform to the type or pattern usually found in somatic disorders of the nervous system". This occurrence of extinction in hysterics is well in line with our hypothesis.

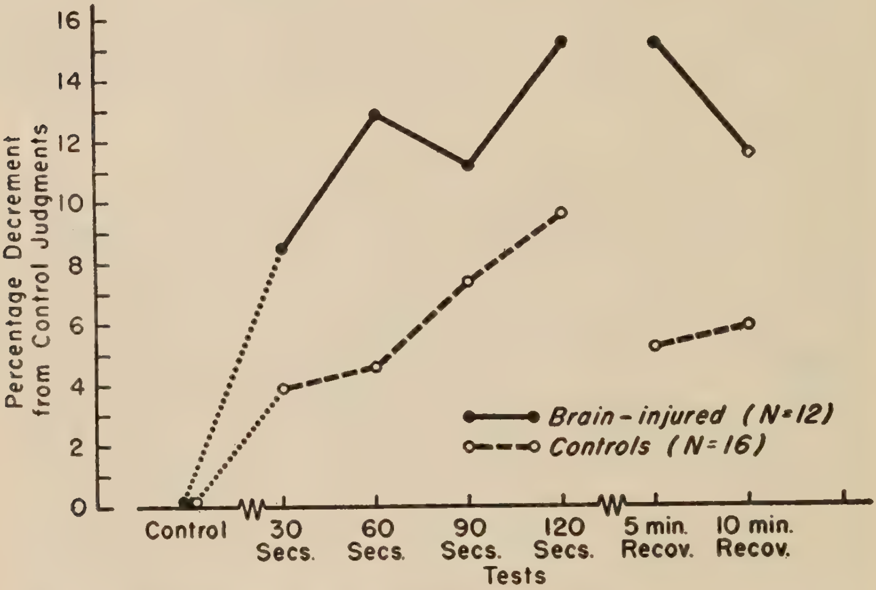

FIG. 6.—Comparisons of rate of development of figural after-effect in brain-injured and controls.

It is also interesting to notice that extinction phenomena could be facilitated or produced through the use of inhibiting drugs such as alcohol or sodium amytal. The general extraverting effect of these drugs is well known, and it appears safe to venture the prediction that quite generally *inhibitory drugs will lower the conditionability and heighten the satiation effects* in experimental subjects, whereas *excitatory drugs will increase the conditionability and lessen the satiation effects* in experimental subjects. Experiments along these lines should be of particular interest as they enable us to actually vary the degree of extraversion-introversion, and thus treat this as an independent variable capable of experimental manipulation.*

Another point of contact between our theory of extraversion-introversion and the effect of brain damage can be found in the exemplary work of Shapiro (1951, 1952, 1953, 1954), who has made use of a model, also derived from Pavlov, which is closely similar to ours. Basing himself on the negative induction phenomena observed by Pavlov, in which excitation of one part of a sensory surface would lead to inhibition in other parts, or in which excitation of one stimulus-response sequence led to inhibition of other stimulus-response sequences, Shapiro carried out a detailed investigation of such phenomena in brain injured and non-brain injured patients, showing that negative induction phenomena were very much stronger in the former than in the latter. Unfortunately there is, at the moment, no experimental evidence regarding the identity or lack of identity of reactive inhibition and inhibition produced by negative induction, and consequently it would be premature to claim that Shapiro's results support the general theoretical framework outlined here. None the less, it seems to the writer that clarification of the relationships obtaining between these different types of inhibition will result in a close integration of these two sets of phenomena. Further research in this sphere appears to be urgently required.

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* Since the above was written, an independent proof has been provided in favour of predictions of this type by C. Shagass (personal communication). Having succeeded in providing an objective sedation threshold for sodium amytal in terms of electroencephalographic changes, Shagass showed that sedation thresholds in terms of Mg./Kg. were low for hysterics (average 2·8) and high for dysthymics (5·0), with mixed neurotics intermediate (3·8). These highly significant findings are exactly in line with our theory; hysterics already near the inhibitory extreme require only a small amount of sodium amytal to reach the threshold. whereas dysthymics, being at a considerable distance from the inhibitory extreme, require a large amount of sodium amytal to reach the threshold.

In pointing out the similarities between extraverted behaviour patterns and those resulting from brain damage, it was almost inevitable that the theory of brain damage developed should be simplified almost to the point of caricaturing the real complexities of the situation. We have discussed this question as if the actual location of the brain damage played no part at all in the determination of the reaction pattern, and while the results of Klein and Krech suggest that severity of damage rather than location is the important consideration, this is almost certainly too simple a view to be acceptable. In some unpublished work, Petrie has shown, for instance, that operations involving Brodman's areas 9 and 10 invariably produce more extraverted behaviour patterns in patients operated on, while operations not involving these areas, such as cingulectomy and orbital undercutting, do not produce such extraverted tendencies to anything like the same extent, if at all. Clearly, a theory of this kind will be required to be made much more specific before it can be clinically useful. However, even at the present stage of knowledge, and even using what is patently an over-simplification, none the less it has proved possible to make varifiable predictions in this field and to support or disprove hypotheses experimentally. In so complex and unexplored a field as this, it would be unreasonable to expect more of any hypothesis in its early stages.

VII

An effort has been made in this paper to develop a hypothetico-deductive theory of anxiety, hysteria, and brain damage. This type of theory is characteristic of scientific endeavour which attempts to go beyond pure empiricism and simple induction to the postulation of laws and general theories, and the deduction from these of both observed and, as yet, unobserved consequences. Such a theory in its early stages is almost inevitably a gross over-simplification of the very complex relationships included within it. Nevertheless, from the point of view of science, it is more useful than more complex and more sophisticated theories, which do not enable one to make clear-cut and testable deductions. It is only in making such deductions and testing them that the value of a theory can be assessed, and it is only through experimental procedures of this type that improvements can be made and greater complexity achieved without loss of rigour.

In addition to presenting the theory, this paper has also presented a number of facts and it should be the task of those who hold alternative theories to that developed here to see to what extent these results could have been predicted in terms of these other theories. To take but one example, psychoanalytic writers lay little stress on the differentiation between the hysterical and the dysthymic types of disorder, declaring that the differences are largely accidental, and that the one may easily turn into the other in the process of therapy. Such a view does not agree with the very profound differences observed in respect to physiological processes, such as conditioning and satiation. If a theory fails to predict observed facts of this nature, then it becomes the duty of those holding the theory to discard it or to amend it in such a way that the new facts are included within it. It would present a particularly interesting test of these psychoanalytic notions if, in terms of the Freudian system, predictions were made as to some of the facts likely to be found in experiments on reminiscence, apparent movement, and so forth, and if these predictions were compared with those made in this paper, and also with the eventual outcome of the experiments which are now in progress. Scientific advance has usually been particularly rapid when alternative theories were available, claiming to account for the same set of phenomena, and when crucial experiments became possible in the sense that phenomena predicted by one theory could not be predicted by the other, or were predicted to occur in a different manner.

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APPENDIX

For the sake of completeness we should add to our account of attempts to link learning theory and personality theory the work of Spence and his colleagues at Iowa. We have already mentioned their demonstration that anxiety, as measured by the Taylor Anxiety Scale, a questionnaire especially constructed from items of the Minnesota Multiphasic Personality Inventory, was correlated with conditionability, and also their hypothesis that this result was due to the high drive value of anxiety. We have also shown that this theory is untenable in view of the lack of conditionability of hysteric subjects.

More recently, Spence and his colleagues have gone on to consider the possible effects of anxiety as a variable in more complex learning situations than are presented by simple conditioning. In an admirable review of all this work, Child (1954) has indicated quite clearly the main line of argument followed by them: "The theoretical distinction they make among various learning tasks has to do with the number of competing response tendencies aroused. In simple conditioning, the situation is so controlled that a single stimulus-response tendency is aroused, with no appreciable competition; here the effect of increased anxiety is simply to improve performance through increasing the drive which, by Hullian theory, enters as a multiplier in determining the strength of this single S–R tendency. But in a more complicated learning task, such as serial rote learning, there are likely to be several competing tendencies present at any one point, and heightened drive will, according to Hullian postulates, have a multiplicative effect upon the strength of all these tendencies. If the correct response is not the one with greatest habit strength, the result will be to increase the advantage in response strength of those incorrect responses which are above it in the response hierarchy. Thus the probability of evocation of the correct response will be lowered, and the persistence of the dominant incorrect responses will be more protracted, so that during this period performance of subjects with high anxiety will be inferior to that of subjects with low anxiety."

The prediction that in situations where numerous incorrect response tendencies are aroused, high anxiety should make for poorer performance than low anxiety, has been borne out in several studies reported by Taylor and Spence (1952), Spence and Farber (1953), Lucas (1952), Montague (1953), and others. In each case, anxiety was measured by the Taylor Scale and the results seem to point quite definitely to some such relationships as that predicted by Spence. There are, however, a number of difficulties on the theoretical level, which make interpretation difficult. Some of these difficulties derive from the same error already noted in connection with Mowrer and with Miller and Dollard, namely, a failure to duplicate on the personality side the exact and careful work carried out on the learning side.

In the first place, then, it must be pointed out that the interpretation of a high score on the Taylor Anxiety Scale is difficult as the derivation of this Scale was largely subjective and psychiatric. Holtzman, Calvin and Bittermann (1952), as well as Deese, Lazarus and Keenan (1953) have found high correlations between the Taylor Scale and scales measuring general neuroticism, and, more recently, C. Franks (1954) has obtained a correlation of ·92 between the Taylor Scale and the Maudsley Medical Questionnaire, which is a measure of general neuroticism. From correlations reported by him between the Anxiety Scale and a variety of other scales, it would appear that, in terms of the two-dimensional framework shown in Figure 1 of this article, the Anxiety Scale has considerable projection on to the neuroticism axis and a slight projection on to the introversion axis. This accounts for the fact that only slight correlations are found between the Taylor Scale and conditioning by Spence and his colleagues, and the fact that Hilgard, Jones and Kaplan (1951) and C. Franks (1954) failed completely to obtain significant relationships between the Scale and conditioning. To obtain such correlations a scale having considerable projections on the introversion scale and slight or negligible projections on the neuroticism scale should have been used. Such a measure is available in the form of Guilford's rhathymia, or R–scale, as shown in *The Structure of Human Personality* (Eysenck, 1953), and our prediction is clearly borne out by the results reported by C. Franks, who found a correlation between eye-blink conditioning and the Taylor Anxiety Scale of ·151 (insignificant), while that between conditioning and rhathymia was −·483. (This correlation is negative because rhathymia is a measure of extraversion; it is, of course, fully significant.)

If this argument be admitted, and if it be agreed that the Taylor scale is largely a measure of neuroticism, then it would seem to follow that whereas ease of conditioning is related to introversion, learning difficulties in complex situations are related to neuroticism, in the sense that the more neurotic a person, the more difficulties will he have in learning the correct one out of a number of possible responses having roughly equal probabilities of occurrence. Again, as in the case of conditioning, the crucial proof of this hypothesis as opposed to that of Spence will lie in the performance of a group of hysteric subjects as compared with normals and with dysthymics. Our prediction would be that hysterics should perform less well than normals, and no better than dysthymics; Spence's prediction would presumably be that they should perform much better than dysthymics (due to absence of anxiety).

A second objection to the theories of Spence has been presented by Child in connection with the experimental studies of Mandler and Sarason (1952). These investigators also used questionnaires of anxiety, but relied for their experimental design mainly on the arousal of anxiety through different test instructions, thus manipulating the independent variable. On the basis of the data collected by them, they arrived at a rather different type of hypothesis from that developed by Spence. In Child's summary, they argue that "high anxiety subjects evidently have habits of responding to anxiety with various responses, internal and external, which are incompatible with efficient pursuit of a complex task; hence these subjects do worse in a situation which evokes much anxiety (through ego-involving instructions, announcement of failure, etc.) than in a situation which does not evoke much anxiety. Low anxiety subjects, on the other hand, evidently lack strong habits of responding to anxiety with task-irrelevant responses, so that anxiety-arousing instructions have as their main effect on these subjects an improvement of performance through increase in drive. (The increase in drive in an anxiety-arousing situation must of course be supposed to occur in the high anxiety subjects also, but its direct effect in improving performance to be obscured through interference by the task-irrelevant responses made to it.)"

Interesting as these Mandler and Sarason studies are, neither they nor a similar one by Waterhouse and Child (1953) can be considered to be in any sense definitive. Again, the failure seems to be largely due to a lack of a taxonomic framework in terms of which results can be interpreted. We are shown that different persons react differently to anxiety producing stimuli, but unless we can specify in terms of some such framework as that given in Figure 1 the position of groups responding thus differently, it becomes exceedingly difficult to generalize the findings or to link them with personality theory as a whole. It is to be hoped that a rapprochement may be achieved in the near future which would enable such a link to be made.

If it be true that the personality variable relevant to the Spence and Sarason studies is that of neuroticism, then we may be able to find an explanation of the findings in terms of the Yerkes–Dodson law (1908). This law, as is well known, specifies that *the more complex a task, the lower the optimum drive level required for its execution.* If we regard a person high on the neuroticism continuum as one in whom autonomic drive levels are particularly high, and particularly easily aroused, whereas in a person low on the neuroticism continuum autonomic drives are at a lower level, and less easily aroused, then it would seem reasonable to predict that increase in autonomic drive level would lead to a decrement in performance on complex tasks in the more neurotic, while it would lead to an improvement in performance in the less neurotic. More exact predictions could only be made in terms of accurate measurement, both of the degree of neuroticism of the subjects taking part in the experiment, and of the degree of drive leading to improvement or decrement of performance respectively. A beginning has already been made in both these directions, but a great deal more experimental work is required before the truth or falsity of this hypothesis can be demonstrated in the requisite quantitative detail.

REACTIONS TO PAIN IN VARIOUS ABNORMAL MENTAL STATES*

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THE study on which we are going to report has its origin in a clinical observation made twenty-six years ago (Schilder and Stengel, 1928).

An elderly female patient whose main symptom was a receptive aphasia, showed a peculiar reaction to painful stimuli. She failed to withdraw from the source of those stimuli, or did so only to a very slight degree, irrespective of the part of the body surface affected. She never showed that tendency to total withdrawal which characterizes normal behaviour. Sometimes she exhibited paradoxical reactions in that she followed the stimuli with her hand as if to invite more pain. There was no indication of a disturbance of perception. That the patient perceived pain could be inferred from her utterances and from wincing, which she often showed very markedly, while at the same time failing to withdraw the afflicted part of her body. This was another argument against the presence of a disturbance of sensation which did not affect the whole body surface. Within a few weeks the aphasia subsided sufficiently to enable the patient to talk about her attitude to the painful stimuli. She definitely experienced them as such but did not seem to mind them. Reactions to certain other stimuli were found to be equally abnormal. Neither a match lit close to her eyes, nor a loud clap, would cause her to withdraw in a normal manner. It did not make any noticeable difference whether these stimuli were sprung on her unexpectedly or whether she could watch them being inflicted, nor did it matter who administered them. In marked contrast to the apparent indifference to external stimuli, the patient was sensitive to internal pains and used to complain in an almost hypochondriacal manner about stomach pain. The same discrepancy was noticed in other cases. The patient's peculiar behaviour in relation to painful or other noxious stimuli inflicted from outside which are usually experienced and reacted to as threats, was assumed to be due to a disorder on a higher level of integration. It was called, perhaps not very aptly, *asymbolia for pain*, the patient, while able to perceive pain, being unable to appreciate its significance as a signal of danger and to react accordingly. The term is obviously not comprehensive enough and does not take into account the patient's failure to respond normally to other external stimuli to which the usual reaction is withdrawal. This behaviour pattern was subsequently observed in a considerable number of cases. Clinical observations suggested that this symptom was related to parietal lobe lesions in the dominant hemisphere, and this was borne out by a series of post-mortem examinations. Asymbolia for pain has since been observed by others and is often referred to among the effects of parietal lobe lesions. However there is still much that is obscure about it. In psychiatric hospitals one can often observe it in cases of brain atrophy in which the parietal, or parieto-temporal area is more severely involved than other parts of the brain. The symptom fits well into the present-day concepts of parietal lobe syndromes (Critchley, 1951). It implies an inability to integrate external stimuli, or, as Schilder put it, to connect the experience of pain with the body image.

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* Based on a paper presented by E. Stengel and A. J. Oldham to the Research and Clinical Section of the Royal Medico-Psychological Association on 12 February, 1953.

Early in the study of this symptom certain similarities with abnormal reactions to pain in patients suffering from mental disorders were noted. Catatonics sometimes show similar behaviour, including the paradoxical reactions. Pain asymbolia has lately been referred to by writers who concerned themselves with the experimental study of pain. It is regularly mentioned in connection with the so-called innate insensitivity for pain, and also with Bender's extinction phenomena, although its relationship to both those anomalies is far from clear.

Dissociation between perception of and reaction to painful and other noxious stimuli is the most striking feature of pain asymbolia, but the patients who show this symptom are not as a rule suitable subjects for elaborate tests requiring intelligent co-operation. This is the reason why this anomaly could not be subjected to systematic experimental investigations. Harold Wolff and his associates, by distinguishing between perception of pain and reaction to pain in suitable experimental subjects have given research in this field new direction and impetus.

We have set out to study with the help of tests the reactions to pain in a group of patients who on clinical examination showed the symptom of pain asymbolia. Until now no attempt has been made to score these reactions. The same tests were employed in several groups of patients suffering from various mental conditions. Having taken note of their motor reactions to pain and to sudden auditory and visual stimuli, we studied their reactions to other types of pain, and tried to correlate them with the motor reactions. We told the patients that they were being tested, and those who showed a disinclination to co-operate were excluded from the series. Most of the tests were not more unpleasant than those carried out in a thorough neurological examination, and the discomfort suffered, if any, was small.

Patients belonging to a wide range of mental conditions have been tested, but they can hardly be regarded as representative samples. We were less concerned with comparing the reactions in various groups of mental conditions, than with the correlations between the various tests. The present investigation is a pilot study aimed at exploring the field and at preparing the ground for more precise experiments. In particular we have as yet no information as to how normal persons react to our tests.

While most previous workers on pain concentrated on perception, we may be criticized for studying reactions only. To evaluate their significance, we ought to be sure of what was perceived. This difficulty is inherent in every study of pain, especially in a case material such as ours. One of us (A.J.O.) actually tried, in a number of cases, to obtain measures of the threshold of perception with the help of the Hardy–Wolff apparatus, but gave it up when he found that the subjects could not offer the necessary co-operation. This is not surprising if we remember the requirements for such investigations laid down by Harold Wolff and his associates. They state that unless their subjects had a detached, unprejudiced and objective attitude, the results are useless. Obviously the bulk of our patients lacked those rather exacting requirements. But even if we could have measured the pain threshold in every one of them, our difficulties would not be over. It is after all the degree of unpleasantness to which the reactions are related, and this is impossible to measure except by the reactions and the patient's subjective estimate. Where we suspect a dissociation between perception and motor reaction we depend entirely on the patient's estimate. But the lack of exact information on the degree of pain experienced by our patients is a disadvantage that can easily be overstated. Our patients were, of course, examined neurologically and we were careful to exclude cases in which there was a suspicion of a disturbance of sensation due to structural damage. And secondly, all the stimuli were well above the threshold level.

In addition to observing the motor reactions to painful stimuli, we endeavoured to study certain physiological responses and to correlate the various reactions to each other. Observations of the pupils and the pulse rate have been found useful by some observers. We found pupillary reactions unreliable and impossible to quantify. The pulse rate could not be studied in our experimental set-up for technical reasons. We employed a test which, though originally designed for a different purpose, has recently been introduced into the study of pain. Immersion of a hand in ice water results in pain and rise of blood pressure. Hines and Brown's cold pressor test is based on these effects. These workers, as well as others, were almost exclusively interested in the effect of local cooling on the blood pressure, although the pain was from the beginning suspected to be of importance in the production of the temporary hypertension. Wolf and Hardy assumed a direct correlation between the degree of cooling, the intensity of pain produced by the cold and the degree of blood pressure rise. In about 60 seconds after the immersion of the hand a painful sensation is experienced. Our subjects were not dissuaded from withdrawing the hand at any moment they chose. Wolf and Hardy consider that the vasopressor effect is related to the pain itself or to the subject's reaction to pain. They regard the latter as more likely and are inclined to relate individual differences in the reaction to cold pain to variations from subject to subject. The pain produced by cooling is of a different type and origin to the painful stimuli administered to the body surface with a pin. It is a deep pain which is not experienced as coming directly from outside.

A kind of pain which is even more felt to originate inside the body is the headache produced by the injection of a small dose of histamine. This method has also been employed in this study of the reactions to pain.

EXPERIMENTAL PROCEDURES

Case Material

The patients tested were selected from cases seen at the Bethlem Royal and Maudsley Hospital, the Fountain Hospital, and Tooting Bec Hospital.

This investigation was in the nature of a field study, and therefore we selected our cases to cover a fairly wide clinical field, with on the whole relatively small numbers of cases in each diagnostic group. The diagnoses at the time of initial testing were as follows:

Group	Diagnosis	Number of Patients
A	Parieto-temporal Syndromes	11
B	Depressive States	14
C	Schizophrenic Psychoses	13
D	Psychoneuroses	8
E	Frontal Lobe Operation Cases	6
F	"Medium Grade" Defectives	10
G	Senile Dementias	10
H	"Low Grade" Defectives, Female	54
I	"Low Grade" Defectives, Male	43

In Group A there was evidence in eight cases of lesions affecting both the dominant parietal and the dominant temporal lobe, while in three cases the dominant parietal lobe only was affected. In none of these cases was there a circumscribed disturbance of sensation.

In Group B, five cases exhibited depression with retardation, eight depression with agitation, while one case showed retardation of speech associated with agitation of behaviour.

In Group C, four patients exhibited catatonic stupor, two cases were hebephrenic, six cases paranoid, and one case unclassifiable into a sub-type of schizophrenia.

In Group D, four cases had a typical anxiety neurosis, three cases were of obsessional neurosis, and one case was of conversion hysteria.

In Group E, there were three cases of obsessional neurosis, two cases of depression and one of paranoid schizophrenia. The cases were tested before, as well as after, operation, and as such were therefore included in the other groups. The operations included Poppen's variety of bilateral prefrontal leucotomy, bilateral topectomy, and bilateral cortical undercutting.

In Group F, five male and five female defectives were selected. The diagnostic heading "medium grade" was used to include imbeciles with I.Q.s ranging from twenty-nine to fifty-one.

The patients in Group G were also selected equally for the sexes, with ages ranging from seventy to eighty-eight. They were selected as having simple organic dementia with no evidence of any localizing cerebral lesions, nor evidence of any "non-organic" psychotic features.

Groups H and I comprised all the patients of one female and one male ward respectively in the Fountain Hospital; the patients included both idiots and low grade imbeciles. These large numbers were selected with certain special problems in mind which we intend to discuss in another paper.

The Tests (see Appendices)

Batteries of tests, which we have for convenience termed "clinical" and "clinico-physiological" were administered to all cases selected in the order indicated below. The "clinical" tests were administered by one of us (A.J.O.). In the "clinico-physiological" battery one of us (A.J.O.) worked together with Dr. Lovett Doust who made the oxymetric recordings which will not be described in this paper.

The Clinical Battery of Tests

Code Number	Laterality	Description
1	R and L	Hard Pin Pricking on Palm of Hand.
2		Hard Pin Pricking of Tongue.
3	R and L	Tickle to Sole of Foot.
4	R and L	Hard Pin Pricking to Sole of Foot.
5	R and L	Pressure to Tibia.
6	R and L	Pressure to Tendo Calcaneus.
7	R and L	Pressure to Supra Orbital Region.
8	R and L	Nasal Probing.
9	R and L	"Clap Test".
10	R and L	"Fist Test".
11	R and L	"Match Test".

The Clinico-Physiological Battery of Tests

Laterality	Description
R	Cold Pressor Test (C.P.T.)
	Histamine Headache Test (H.H.T.)
R	Soft Pin Pricking of Palm.
R	Hard Pin Pricking of Palm
R	Hard Pin Pricking of Cheek.
R	Nasal Probing.

The tests were administered to one or both sides of the body as indicated above.

Each clinical test was scored on a five point scale from 0 to 4 for each of three modes of reaction namely withdrawal movement (M), wincing (W), and subjective experience (S), as described in detail in the appendix.

The patients in Groups A to D, F, and G, were each given the battery of "Clinical" tests followed within three days by the "clinico-physiological" tests. In Groups F and G, however, the H.H.T. was omitted for administrative reasons.

Retesting of patients was performed in most cases in Groups A and D but not in the other groups, except, of course, in Group E where the patients were tested during the week before operation and retested three weeks after.

The Groups H and I were given only tests 1 and 9 of the clinical battery, and in addition tests involving hard pin pricking to both cheeks and to both thighs (medial aspects).

RESULTS

I. The Clinical Battery of Tests

The data discussed in this section are the scores for withdrawal movement (M), wincing (W), and subjective experience (S), on the twenty-one "clinical" tests (tests 1 to 11, R and L). For each of the six diagnostic groups of patients given these tests (A to D, F and G), the scores were set out in an analysis of variance in order to isolate:

(1) Systematic differences between the mean scores of the individual

patients for all the tests, between the mean scores for their modes of response (i.e. M, W, and S), and between the mean scores of the eleven tests.

(2) "Interactions" (i.e. differential effects) of patients and modes, of patients and tests, and of modes and tests. This would take into account the differential reactions to various tests and modes.

(3) The residual unsystematic variations, i.e. those which are not accounted for by (1) and (2).

It should be noted that, just as in much work of this kind, the patients in each diagnostic group were not sampled at random from some larger specifically defined and physically existent population of patients. Statistical tests of significance are therefore not called for; but it will be seen that there is no difficulty in establishing the generality of the findings.

TABLE I

Illustrative extract of the data

Movement (M), Wince (W), and Subjective (S) scores on the pressure tests 5R and 5L for group A, together with the mean on all tests

Patient	Right Tibia (5R)			Left Tibia (5L)			Means for Test 5	Means on all Tests
	M	W	S	M	W	S		
1 ..	1	1	1	1	1	1	1·0	0·8
2 ..	2	3	2	3	3	2	2·3	1·2
3 ..	0	1	0	0	1	0	0·3	0·4
4 ..	1	1	1	1	1	1	1·0	0·9
5 ..	0	1	1	0	1	1	0·7	0·7
6 ..	3	3	3	3	3	3	3·0	2·7
7 ..	2	3	1	2	3	1	2·0	2·4
8 ..	2	2	3	2	2	3	2·3	2·4
9 ..	1	2	(1)	1	2	(1)	1·3	0·9
10 ..	2	2	3	2	2	3	2·3	2·1
11 ..	3	3	(3)	3	3	(3)	3·0	2·6
Means ..	1·6	2·0	1·7	1·6	2·0	1·7	1·8	1·6

N.B.—No subjective readings were available for the patients 9 and 11; in general, up to 10–20 per cent. of the scores could not be recorded. For simplification in analysis, the missing values have been estimated by an approximate "missing-plot" technique; these estimates do not, of course, affect the conclusions.

(a) *The Test Differences.* A comparison of the individual response scores of all those tests administered to the right and left sides of the body revealed an almost complete equality in all cases. This is illustrated in a typical extract of the data, given in Table I, where the only R–L discrepancy, in the M scores of the second patient, is likely to be merely an error of recording. Such an exact correspondence between right and left responses may have been due to the method of testing because the examiner performed each test on the right and left side respectively before recording the responses. Essentially, therefore, we are dealing with only the mean scores of those eleven tests which are summarized in Table II. It will be seen that the tests differ at most by about one unit in average scoring level, and that these differences can mainly be traced to differences in the type of stimulus (i.e. pin prick, pressure, etc.). An exception to this is the tongue pin-pricking test (2), whose mean score is 0·7 units less than that of the sole pin-pricking test (4) (see also under "modal differences" below). The main body of Table II is given to illustrate the regularity of these findings for the different diagnostic groups.

TABLE II

Average Test Scores of the Diagnostic Groups

Tests and Test Numbers

Group	Number of Patients	Pin Prick			Pressure			Threats			Tickle	Nasal Probe	Means
		1	2	4	5	6	7	9	10	11	3	8	
A	11	1·7	1·0	2·1	1·8	1·7	1·9	1·4	1·4	1·2	1·4	1·6	1·6
B	14	1·8	1·5	2·4	1·9	1·9	1·8	1·8	1·8	2·1	1·5	1·7	1·8
C	13	1·7	1·5	2·3	1·9	2·0	2·0	1·3	1·4	1·7	1·5	2·0	1·8
D	8	2·4	2·2	2·6	2·0	2·4	2·6	2·0	1·1	1·7	1·9	2·0	2·1
F	9*	2·1	1·9	2·3	1·7	1·9	2·1	1·9	1·7	2·5	1·9	2·0	1·9
G	9*	2·2	1·5	2·4	2·0	2·2	2·6	1·7	1·7	1·7	1·2	2·2	1·9
	Means	2·0	1·6	2·3	1·9	2·0	2·2	1·7	1·5	1·8	1·6	1·9	1·9
Retested A to D	27	2·1	1·6	2·2	1·8	1·9	2·1	1·5	1·3	1·6	1·4	1·9	1·8

* One patient of the original 10 refused all tests.

It should be mentioned that tests 1 and 5 were repeated with the patients' eyes open and shut respectively. The response scores of all patients so tested (Groups A, D, F, G) showed no difference of any degree.

(b) *The Modal* (*M*, *W*, *S*) *Differences.* The differences in average scoring level for the three modes of response to any test, are nearly all very small, as may be seen from Table III. The modal differences do, however, vary consistently with the kind of stimulus, and like the test differences, they are very consistent for the six diagnostic groups (A to D, F and G). For the pin-pricking test of the tongue, test 2, the modal differences are such that the scoring for withdrawal movement is almost at the same level as for those scores for the two other pin pricking tests, and it is the average wincing and subjective responses which are lower and thus give rise to the difference in mean score noted above.

TABLE III

Average Differences for the three modes, Movement (M), Wince (W) and Subjective Response (S)

Tests and Test Numbers

Group	Number of Patients	Pin Prick 1 and 4		Pin Prick 2		Pressure 5, 6 and 7		Threats 9, 10 and 11		Tickle 3		Nasal Probe 8	
		M–W	W–S	M–W	W–S	M–W	W–S	M–W	W–S	M–W	W–S	M–W	W–S
A ..	11	−0·1	0·1	0·8	−0·3	−0·4	0·2	0·0	0·1	0·0	0·5	0·3	0·0
B ..	14	0·0	0·1	0·5	−0·2	−0·5	0·2	−0·1	0·3	0·6	0·6	−0·2	0·8
C ..	13	0·5	0·0	0·8	−0·2	−0·3	0·0	0·0	0·0	0·2	0·5	0·5	0·0
D ..	8	−0·2	0·5	1·0	0·0	−0·3	0·5	0·0	0·3	0·2	0·0	−0·3	0·2
F ..	9*	0·3	1·0	0·5	0·4	0·0	0·5	0·0	0·3	0·0	0·6	0·3	1·0
G ..	9*	−0·2	0·2	0·5	0·0	−0·4	0·2	0·0	0·7	0·4	0·0	0·0	0·0
	Mean	0·1	0·2†	0·7	0·2†	−0·3	0·2†	0·0	0·3†	0·2	0·3†	0·1	0·2†
Retested A to D	27	0·3	−0·1	0·9	−0·4	−0·3	0·2	−0·1	0·3	0·3	0·0	0·3	0·4

* One patient of the original 10 refused all tests.
† W–S difference for group H excluded (see text).

Another exception to the general pattern occurs in Group F, the "medium" grade defectives, whose subjective scores are consistently lower than the corresponding scores for movement (M) and wincing (W), but the subjective estimates of such mentally defective patients were at the time considered unreliable.

(c) *Differences between Individual Patients.* By far the largest source of variation in the responses was found in the individual differences between patients. These are illustrated in Table I in which the mean scores for test 5, averaged over the three modes of response, can be seen to vary from 0·3 to 3·0 units among the different patients in Group A. A comparison of these means with the corresponding mean scores for all eleven tests (last column Table I) shows that the variation in the responses of individual patients in Group A is a consistent one for the whole test battery. Individual differences between patients in the other diagnostic groups behaved in the same consistent manner.

This general picture of consistent individual differences is, however, complicated to some extent by the presence of certain interactions between patients and tests, and between patients and modes of response. Thus in Table I it can be seen that patient (2) scored 2 or 3 for test 5 (and incidentally also on the other two pressure tests 6 and 7) whilst his mean score of 1·2 on all the tests indicated a lower general level of scoring. Again, patient (3), scored systematically lower for the M and S modes of test 5 (and of test 6) than was indicated by scoring on the other tests. These patient-test interactions were generally of the order of 1 unit or less, while the patient–mode interactions were usually smaller still. They occurred in about 10–20 per cent. of the data, appearing rather haphazardly—not, for example, more for high scores than for low—so that their detailed description is unnecessary.

(d) *Differences between the Diagnostic Groups* (*A–D, F and G*). The mean test score for each diagnostic group is shown in the last column of Table II. From this it can be seen that the largest difference in mean scores, i.e. 0·5, is that between the organic group of patients (A), who had the smallest mean response score, and the psychoneurotic group (D), who produced the largest: but even this difference is negligible when the large individual differences between patients are taken into account.

(e) *Sex Differences.* A comparison of the response scores of male and female patients in groups A to D, F and G, to the clinical battery of tests showed the male patients to score consistently 0·2 or more units higher than the females. In view of the large individual response variations, this difference for any one group of patients would be of no account, but its consistency in all the groups of patients makes it worthy of comment. This difference could not be traced either to specific tests or modes and is, therefore, such as it is, a general one.

(f) *Residual Errors.* In the foregoing paragraphs we have described the systematic sources of variation in response. When these were eliminated, the residual unsystematic error variances for the six diagnostic groups of patients (A to D, F and G) were found to be 0·23, 0·16, 0·05, 0·15, 0·14 and 0·15 respectively, averaging to about 0·16 or to a standard error of 0·4. Apart from the 10–20 per cent. individual discrepancies mentioned above, therefore, most of the scores on the different tests and modes are accurately described to within about half a unit by the systematic differences described above.

(g) *Retest Results—Immediate.* As mentioned above, all patients in Group A to D were given the clinico-physiological battery of tests within three days of the clinical battery. By this procedure, tests 1 and 8 of the clinical battery were repeated within a period of three days during which time the patients maintained a relatively unchanged mental state and no treatment was given. The response scores from these two tests and retests agreed very closely with those of the initial tests.

Longterm. The Clinical Battery of Tests was repeated after periods varying between two weeks and three months to patients in Groups A to D. For administrative reasons, only 27 of the 46 patients were retested, and the rather disjointed data which resulted have not been analysed in any great detail. However, two features of the retest data are fairly clear cut.

Firstly, it can be seen from the last lines of Tables II and III that the initial patterns both of the test and of the modal differences were closely reproduced in the second test.

Secondly, the initial test and retest scores averaged over all the tests showed no trends upward or downward, and the standard deviation of the individual differences was 0·7, corresponding to a "standard error of measurement" of about 0·5. Since the individual mean scores ranged from 0·3 to 3·0 (S.D. about 0·8) this would represent a reliability coefficient of about 0·6. These test-retest discrepancies were too large to be accounted for in terms of the residual "error" variation at each application of the battery of tests, and therefore indicate systematic changes in individual scoring level. Nevertheless a tendency for high initial scores to be followed by high retest scores is indicated; for example the average scores of only 6 out of 27 patients retested showed a change of from below 2·0 to above 2·0 units or vice versa. (Some of the test–retest discrepancies are related to changes in "Overt Reactivity" as described below.)

(h) *Prefrontal Operations*. The six patients in Group E tested before and after prefrontal operations showed an average response score change of less than 0·5 units except for one patient who on post-operative testing scored nearly 2 units higher. Estimates of "Overt Reactivity" (see below) in these patients also showed no post-operative change except for two patients in whom a pre-operative estimate of "increased overt reactivity" changed post-operatively to one of "intermediate overt reactivity". From these results it would appear, therefore, that the six patients tested three weeks after operation showed practically no change either in their reactivity to painful and non-painful stimuli or in their "overt reactivity", from their pre-operative condition.

(i) *Hypnosis*. In one case, Mrs. P.R., aged 32 years, diagnosed Conversion Hysteria, it was found easy to induce a state of deep hypnosis. The Clinical Battery of Tests was then given to her under the following conditions:(i)Hypnotic suggestion of total anaesthesia; (ii) Hypnotic suggestion of total analgesia; (iii) Hypnotic suggestion to the effect that she would experience the painful and non-painful stimuli, but that they should not worry her; (iv) Fully conscious.

It was noted that under conditions (i) and (ii) the patient's responses were consistently of an equally low order (about 0·3 units). Under condition (iii) the patient consistently responded by about one unit more than for (i) and (ii), while under condition (iv) she scored about 3·0 units consistently for the M, W, and S responses to all the test stimuli.

It was further noted that under conditions (i) and (ii) the patient gave no subjective responses, her modes of response being predominantly those of withdrawal movement (M), except for the pressure stimuli to which she also reacted by wincing (W), whereas under condition (iii) she responded by all modes (M, W, S) to almost all the tests.

From these results the following conclusions would seem indicated:

1. When awake, the patient reacted strongly to all the clinical test stimuli by all modes of response.

2. When given the hypnotic suggestion that she would feel the stimuli but not be worried by them, she reacted in a similar manner but to a markedly lesser degree.

3. When given the hypnotic suggestion that she would feel no pain, or that she would feel nothing at all, she stated that she felt nothing (S), although she reacted slightly to the test stimuli by withdrawal (M) and wincing (W).

Summary of Results from Clinical Test Battery

1. No difference was found between the reactions of the right and left sides of the body.
2. Individual differences on the different tests or modes tended to be very consistent (apart from some occasional and relatively small individual interactions with specific tests or specific modes), the unsystematic residual error variation also being relatively small.
3. The range and general level of scoring in the different diagnostic groups were very similar.
4. The retest results generally showed little change even after different therapeutic regimes had been carried out. Retesting six patients three weeks after a prefrontal operation showed practically no change of reactivity.
5. Male patients reacted a little higher than female patients.
6. Hypnotic suggestion of anaesthesia, analgesia and "apathy", produced marked alterations in the reactivity of an hysterical patient from that of her waking state.

II. "Overt Reactivity" (O.R.)

The psychomotor behaviour of every patient in Groups A to D, F and G, was assessed by one of us (A.J.O.) outside the test situation. This assessment was made 24 hours preceding the tests. The categories of overt reactivity were as follows:

1. Increased O.R.	Grossly hyperactive and/or tense.
2. Decreased O.R.	Grossly hypoactive and/or apathetic.
3. Intermediate O.R.	Cases not classified (1) or (2) above.

The term hyperactive is to some extent self-explanatory. They were patients whose behaviour at the time they were examined showed some degree of restlessness and a tendency to react strongly to external stimuli of all kinds. An attempt was also made to assess the premorbid behaviour in patients of Groups A to D for overt reactivity; people who, according to the information available, had been lively, anxious and tense within normal limits, were rated hyperactive. On the information available, such classification was difficult and unreliable, but the pattern of "overt reactivity" assessment from the premorbid personality combined with that at the time of first testing seems sufficiently interesting to merit description here. This pattern is shown in Table IV, in which it can be seen to vary from group to group. Perhaps the most striking features here, are to be seen in Group D (psychoneurotics) on the one hand, almost all of whom were rated to show "increased overt reactivity" both in their premorbid and morbid assessments, and in Group A (organic), on the other hand, where at the time of testing the majority of patients were rated to have "decreased overt reactivity", while none had been so rated on their premorbid behaviour.

Turning now to the relationship for each patient between the "overt reactivity" at first testing and the mean response score for the battery of clinical tests, it is seen that the patients rated to show "increased O.R." have a mean response score of 2·2, those rated to show "intermediate O.R." have a mean

TABLE IV

Overt Reactivity Assessments for premorbid behaviour and for that at the time of testing

	Premorbid Overt Reactivity*									
	A		B		C		D		F†	G†
O.R. at time of testing	Hyper.	Interm.	Hyper.	Interm.	Hyper.	Interm.	Hyper.	Interm.		
Increased	1	1	2	6	1	1	7	1	2	1
Intermediate	1	1	1	1	0	5	0	0	8	6
Decreased	3	4	1	2	1	3	0	0	0	3

* Only three patients in all fell into the premorbid hyporeactive class, and are ignored here for simplicity.

† No premorbid records available.

response score of 1·8, while those rated "decreased O.R." have one of 1·2. The standard deviation for the mean response scores for each class of "overt reactivity" is relatively small, about 0·65. This relationship is not seen in the patients of Group F and G. Nearly all of these, however, were rated to show "intermediate O.R." (see Table IV) and the numbers would thus be too small for any general relationship with the response scores—should it exist—to show itself. For Group A to D, therefore, a clear relationship was found between the "overt reactivity" of the patients and their reactivity to the clinical test stimuli.

The 27 patients who were retested with the Clinical Test Battery, were also reassessed at the time of retesting for "O.R.". It was noted that about half of these patients initially assessed to show "increased O.R.", and half of those initially assessed to show "decreased O.R.", became "intermediate O.R." on retesting. None of those patients initially assessed to show "intermediate O.R." changed at the time of retesting. This would seem to reflect a clinical improvement in the behaviour of a number of the patients retested, if we take the "intermediate O.R." assessment to correspond with normality.

Looking at the "O.R." retest assessments and the retest responses on the clinical tests, very much the same relationship as in the initial testing is found: the mean clinical response scores of the patients assessed as "increased O.R.", "intermediate O.R." and "decreased O.R." now are 2·0, 1·8, and 1·1 respectively, compared with the earlier values 2·2, 1·8, and 1·2.

The same kind of relationship—necessarily very small and indefinite, but of particular interest—is found in the individual initial and retest scores on the clinical tests of those patients whose "O.R." assessment changed. Thus the clinical test scores of patients whose "O.R." assessments changed from "increased" to "intermediate" dropped by an average of 0·2 units whilst those of the patients moving from "decreased O.R." to "intermediate O.R." rose by 0·2 units.

Therefore it has been found that the clinical test response scores were generally correlated with "O.R." assessments, both as regards individual differences between patients and as regards any changes in a single patient. Thus, a patient rated to show "Increased O.R." would tend to react relatively strongly to the painful and non-painful test stimuli, and furthermore, if on a later occasion he were assessed to show "intermediate O.R." his reaction to the test stimuli would have diminished accordingly.

III. The Clinico-Physiological Test Battery

Two of the clinical tests used in this battery, i.e. hard pin pricking of the right palm, and probing of the right nostril, had already been used in the clinical test battery, and the responses of individual patients to these paired tests showed close similarity as already described (Ig). The other clinical tests of this battery were unlike any of the clinical test battery, and are irrelevant to this paper.

THE COLD PRESSOR TEST (C.P.T.) AND THE HISTAMINE HEADACHE TEST (H.H.T.)

The detailed administration of these tests is described in Appendix II. Firstly a basal blood pressure level was ascertained. Then in the C.P.T., after immersion of the right hand, four blood pressure readings were made at one-minute intervals, and after withdrawal of the hand, further readings were made every minute until a basal level had been regained. In the H.H.T., similar blood pressure readings were made after the intravenous injection until basal levels had been regained.

The four C.P.T. readings were somewhat variable, but, since they showed no systematic trends, a simple average sufficed to describe them. The H.H.T. was, in contrast to the C.P.T., not of controlled duration, so that the average of any specified number of readings could not be taken. But it was possible by inspection of the data to make a reasonably good estimate of the average effect (i.e. one not contaminated by the later readings which usually approximated towards the initial base line). A rigorous and detailed analysis of this kind of data, involving their statistical treatment as "time series", would be laborious and quite unnecessary here, in that the conclusions made below would not have been affected.

One general comment, however, is required. There is a tendency prevalent in current research to adopt the *maximum* reading during the stress as the criterion of the "stress response". This practice can be very misleading, since such a stress response is influenced, not only by the systematic changes, if any, which should be described, but also by the number of readings taken, which is quite arbitrary, and by the more or less random variability of the readings. For example, even if there is no systematic response at all, the maximum reading during the stress period will of course be higher than the base level; reporting the maximum change would, therefore, quite wrongly suggest that there had been a systematic stress response.

The results of the C.P.T. and H.H.T., so considered, are as follows: The systolic and diastolic blood pressures were highly correlated, as is usually found. The great majority of base level readings for systolic blood pressure averaged 50 units less than those for the diastolic ones. For six patients with high systolic blood pressures, of 200 or more, the pulse pressure was, however, between 75 and 100 units.

For both systolic and diastolic blood pressures, the average increase during the C.P.T. was about 15 units, this being approximately the same for Groups A to D, F and G. Most individual responses lay between about 10 and 20 units, but about one in eight of the patients showed less than 5 units increase, while about the same proportion of patients showed an increase of over 30 units. Those patients who were retested showed responses closely similar to the initial ones.

The H.H.T. was found to give much less consistent responses than the C.P.T. Over one-third of the patients tested showed no systematic blood pressure changes at all and for almost another third, the blood pressure *decreased* from the base line often by as much as 20 units or more. The test-retest results were also rather inconsistent. From these results it would seem either that the experimental technique was not under good control, or that there existed large and unreliable individual differences in the histamine response.

Neither the C.P.T. nor the H.H.T. responses were found to correlate with the mean scores from the clinical test battery. This lack of correlation is not surprising for the C.P.T. in view of the absence of large individual differences. In the case of the H.H.T. where large individual differences were found, however, this lack of correlation is perhaps a further indication of the unreliability of the test.

Discussion

Unlike other workers in this field we have in this investigation utilized a number of different painful stimuli, the reactions being measured in several different ways. In spite of some complexity the results appear to be consistent and seem worthy of comment.

The Clinical Tests. The response scores of the different tests indicate that the response of a patient to any given stimulus depended even more upon his individual reactivity than on the nature of the stimulus. The close similarity of test response scores repeated on the same patients at intervals of three days and after longer periods demonstrates both the technical reliability of the tests and the absence of any marked changes in individual reactions.

The Modes of Response. The differences between the withdrawal movement (M), wincing (W), and subjective experience (S) responses among all the patients tested were in general very small. It seems at first sight to suggest that the behavioural reaction corresponded to the degree of sensation perceived. However, in none of the cases was there evidence of a disturbance of perception. We suspect, therefore, that there was a tendency on the part of the patients to assess the degree of unpleasantness of the painful or threatening sensation by the degree of their motor reactions as has been suggested by Mayer-Gross and Guttmann (1943), and Zilboorg (1948), and Medvei (1949).

The Individual Patients. The differences between the responses of individual patients to the clinical test battery were large. This observation recalls similar findings in which the Galvanic Skin Response was used as the index of reaction to a painful heat stimulus (Hardy *et al.*, 1943, Furer and Hardy, 1950) ; and in which the reaction to a heat stimulus was gauged by the degree of facial wincing and withdrawal (Chapman, 1944; Chapman and Jones, 1944; Chapman *et al.*, 1947). These workers used as their index of reactivity the pain reaction threshold, i.e. the smallest pain stimulus producing a reaction, whereas in our study the degree of reaction was estimated. The indices of reactivity obtained by these two methods are probably correlated but direct study is, of course, needed to verify this point.

Laterality and Reaction. There was no difference between the right and left side of the body regarding the reactions to the clinical test stimuli. As far as this evidence goes it indicates that the dominant side of the body does not react to a greater degree than the non-dominant side.

The Role of Attention. The presence or absence of visual attention appeared to make no difference to the reaction of patients to two of the clinical tests. Critchley (1934, 1949, 1951), when discussing tactile inattention phenomena associated with lesions of the parietal lobes, has suggested that the phenomenon of asymbolia for pain described by Schilder and Stengel (1928) might in fact be due to a bilateral inattention associated with bilateral parietal lesions.

Critchley has further pointed out, however, that the inattention phenomena of parietal lobe lesions are abolished by visual attention. Since the latter had no effect on the reactions of any of our patients with tempero-parietal lesions showing asymbolia for pain, our observations failed to support Critchley's hypothesis. Furthermore, an alteration of attention seemed to play no part when the reaction to pain was altered by hypnotic suggestions, since the latter were made to refer to the sensations which the patient would experience in the hypnotic state, and his attention was kept focussed on the stimulus in all the hypnotic tests.

It appeared, however, that attention played some part in the reaction of psychoneurotic patients. They seemed to anticipate the severity of the coming stimulus to a considerable degree; possibly their attention had been heightened by conscious or unconscious associations with the test situation (Hemphill *et al.*, 1952).

Sex. Various workers (Chapman and Jones, 1944; Kennard, 1952) have reported higher pain perceptual thresholds for men than for women and Hall and Stride (1954) have also observed higher pain reaction thresholds in men. Our findings concerning the degree of reaction showed, if anything, a small tendency for men to react more than women.

Age. The detailed correlation between age and pain reactivity has not been considered in this study because of the small numbers of patients in each diagnostic group, but in view of the similarity of responses between the groups of young medium grade defectives, the psychoneurotics, and the senile dements, which include patients in the first and second, third to fifth, and seventh to eighth decades respectively, it would appear that age alone was not a dominant factor.

"*Overt Reactivity.*" This term has been used by us to describe the degree of psychomotor reactivity of a patient at any given time. Our findings have shown a clear relationship between "Overt Reactivity" of a patient and his reactions to the clinical tests. The factor of "overt reactivity" is therefore of considerable importance, although hitherto it has received little or no attention. Inherent in "Overt Reactivity" is the patient's general reactiveness to all types of stimuli, and it would seem probable from our results, therefore, that the degree of a patient's response to a painful or threatening stimulus is largely determined by his state of general reactivity. This is one of the results of our investigation which it is hoped will be further explored experimentally.

Prefrontal Operations. Prefrontal leucotomy is often followed by a diminished emotional reaction to internal pain (Falconer, 1948; Watts and Freeman, 1948) but an increased physical reaction to external painful stimuli has been described (Columbia–Greystone Associates, 1949) and has been attributed to a lowered pain reaction threshold (Chapman *et al.*, 1948, 1950). In our small series of cases subjected to one of three types of prefrontal operation, no increase in reaction to pain was noted three weeks after operation. However, one could expect a patient following prefrontal leucotomy to react less, not more, to painful stimuli owing to some degree of emotional apathy resulting from the operation. This, in fact, may be true, as the observations of Chapman and his co-workers (1948, 1950) only relate to the rapidity with which a patient starts to react (reaction threshold), and not to the degree of his reaction. This difference is an important one, as it is conceivable that a patient after leucotomy might, due to a lacking of inhibition, withdraw early from a painful or threatening stimulus and yet take no marked avoiding action from a stimulus of greater degree such as those employed by us. It is noteworthy that in our cases there was little evidence of the emotional change which may be expected to follow prefrontal operations, i.e. there was no post-operative diminution in "Overt Reactivity".

Psychiatric Diagnosis. We found no difference between the pain reactivities of any of our six diagnostic groups of patients. This finding would at first sight appear to differ from that of other workers in this field, but we believe that a more careful analysis reveals the reason underlying this apparent discrepancy, and we consider this reason to be important. In the first place, patients falling under the same diagnostic heading will, of course, differ in certain aspects of behaviour. Thus, a depressive state may exhibit agitation, retardation, or a mixture of both. If, according to our findings on "overt reactivity", a group of depressed patients equally divided into agitated and retarded sub-groups were tested for pain reactivity, we should expect such a group to show considerable internal variation but no average deviation from other diagnostic groups, as was, in fact, found in our depressed patients. If, however, pain tests were to be performed upon two different groups of depressed patients, one agitated and one retarded, we would expect the former to react to a significantly greater degree than the latter. This hypothesis, if verified, might well explain the findings of Hemphill *et al.* (1952) which revealed a raised pain reaction threshold in a group of endogenous retarded depressions but no significant deviation of the average pain reactivity in a mixed group of agitated and retarded depressives although there was much internal variation in the latter group. This factor of "Overt Reactivity", we believe, may underly the types of pain reaction seen in all our diagnostic groups of patients.

A number of authors have observed psychoneurotic patients to show a lower pain reaction threshold or a greater degree of reaction than normal subjects (Chapman *et al.*, 1944, 1946, 1947; Hemphill *et al.*, 1952; Malmo, Shagass *et al.*, 1948, 1949, 1949b, 1951a, 1951b). These findings were corroborated by Schilling and Musser (1948) who, however, found the same increase in pain reactivity in patients with menopausal and peptic ulcer syndromes. Hall (1953) has commented on this as follows: "It would seem, therefore, that the lowered pain reaction thresholds shown by these various groups of patients are due to some general factor of emotional disturbance." We would suggest that this factor may be related to our observations on "Overt Reactivity" which one would expect to be increased in the majority of psychoneurotics with anxiety symptoms. On the other hand, we should expect a case of conversion hysteria showing an attitude of "belle indifférence" to manifest a decreased rather than an increased reactivity to pain since the overt reactivity of such a case would probably be diminished. This, we feel, is borne out by the hypnosis tests on one of our patients who under hypnotic suggestions of anaesthesia and analgesia reacted to pain in a manner similar, perhaps, to a conversion hysteric presenting these symptoms.

Cases of chronic schizophrenia have been noted by various authors (Lewis, 1923; Shattock, 1950) to show a degree of physiological underactivity. This has been attributed by Hoskins (1946) to a defect of adaptive efficiency inherent in the process of schizophrenic withdrawal. A diminished reactivity to painful stimuli has also been noted in chronic schizophrenic patients (Malmo, Shagass *et al.*, 1951a, 1951b; Hall and Stride, 1954) but the Montreal workers found the reverse to be true for early schizophrenia (Malmo and Shagass, 1949). Similarly, Bender and Schilder (1930) using faradic stimuli further noted that schizophrenics in catatonic stupor reacted very little while other schizophrenic patients not in stupor reacted within normal limits. These apparently conflicting findings might also be explained in terms of "Overt Reactivity". Thus the "overt" and hence the pain reactivity of the chronic schizophrenic patient would in the majority of cases probably be lower than in cases of early schizophrenia, and one might expect the same relationship to distinguish the phases of catatonic excitement and stupor.

In our schizophrenic group there was a mixture of catatonic, hebephrenic, and paranoid cases with varying degrees of "Overt Reactivity", and it is, therefore, not surprising that the group showed no average deviation of pain reactivity, and that large individual variations in pain reactivity were present.

Our findings indicate that the factor of "overt reactivity" was of considerable importance in relation to the pain reactivities of cases of parieto-temporal syndromes. The latter group included cases with a diminished reaction to pain who thus showed the phenomenon of "asymbolia for pain" as first described by Schilder and Stengel (1928a, 1928b, 1931a, 1931b) in cases with parietal lobe lesions and subsequently observed on numerous occasions. It was this observation which, as mentioned in the introduction, led to the present study (Stengel, 1943, 1944, 1947, 1948; Hemphill and Stengel, 1940; Rubin and Friedman, 1948). The fact that all our patients with parieto-temporal lesions did not exhibit asymbolia for pain does not invalidate the observations of Schilder and Stengel, but it appears now that the phenomenon of pain asymbolia can be expected only in patients with diminished "Overt Reactivity". The whole problem of pain asymbolia, therefore, requires re-examination. It is plain from the literature (Critchley, 1951) that not all cases with parietal lobe lesions have asymbolia for pain, while there is other evidence (Oldham, 1953) that this phenomenon may in some cases be of only temporary duration. It seems that for this symptom to arise a certain constellation of behaviour embracing a diminished "Overt Reactivity" is required, which is present in only certain cases with lesions of the parietal lobes.

It has often been assumed that idiots and imbeciles do not react to pain or do so only to a slight degree, but such a generalization is not supported by the findings presented here. We observed several cases among the low-grade defectives who showed an apparent indifference to self-injury but these patients did not all react sluggishly to painful stimuli applied by us. It would appear that pain inflicted from outside is reacted to differently than that which is self-inflicted, but it is also possible that some of the observations by other workers were made on cases of congenital insensitivity to pain in mental defectives. It is worthy of note that E. Popper (1920), in discussing the apparently diminished pain sensitivity of mental defectives, expressed the view that it might be related to torpidity and apathy in those cases. We intend to present a detailed report of our findings in mental defectives on another occasion.

Diffuse Cerebral Atrophy. In view of the fact that our groups of senile dements and low grade defectives showed little deviation in pain reactivity from other groups of patients, we can only conclude that diffuse cerebral atrophy *per se* has no general effect upon pain reactivity. From our findings, however, it would appear that should a case of cerebral atrophy be associated with an alteration of "overt reactivity" it might indirectly result in an alteration of pain reactivity.

The Cold Pressor (*C.P.T.*) *and Histamine Headache* (*H.H.T.*) *Tests.* In our study the blood pressure responses in the C.P.T. were found to show relatively little variation from one patient to another, while the responses of the H.H.T. were found to be unreliable. There was no correlation between the varying subjective estimates of the pain experienced by our patients and their blood pressure responses. Our findings, therefore, would seem to be at variance with those of other authors (Hines and Brown, 1933; Wolff and Hardy, 1943; Clark *et al.*, 1943). However, differences in technique make a comparison between our results and those referred to above uncertain. Our patients were given the C.P.T. and H.H.T. sitting up instead of lying down as is usual, in order that capillary oximetric recordings might be carried out by Dr. Lovett Doust during the periods of cold pain and headache. How important this postural factor may be we do not know. Wolff (1951) and Igersheimer (1953) have observed alterations of the Cold Pressor Response. Igersheimer reported an average response of 15 to 20 units in psychoneurotics, which agrees with our findings, but rather smaller responses for schizophrenic and manic-depressive patients. Possibly selection factors as well as differences in technique are responsible for this discrepancy.

It is noteworthy that the responses of our patients to the clinical battery of tests did not correlate to the blood pressure responses of the C.P.T. These observations show that either the types of pain inflicted in these two test regimes are different or that, at least in the experimental setting in which our investigations were carried out, the blood pressure responses and the responses to the clinical tests do not conform generally. But this will have to be investigated directly.

Conclusions

An experimental study of the reactions to pain and other noxious stimuli in various abnormal mental states has been presented. It has been found that an individual subject would tend to react similarly to the various test stimuli; that individuals did, however, differ markedly from each other in their reactions; and that both the statistical distribution of these individual differences and the relations between the reactions to the different tests were independent of the type of mental disorder present. The reactions were found to be correlated to the patient's "Overt Reactivity" which in turn was related to the clinical state at the time of testing.

Acknowledgments

We are indebted to Dr. L. I. Hilliard, Physician Superintendent of the Fountain Hospital, for permission to examine mental defectives, and to Dr. J. E. S. Lloyd, Physician Superintendent of Tooting Bec Hospital, for permission to examine patients under his care. We also wish to express our gratitude to Dr. J. Lovett Doust for friendly co-operation.

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APPENDIX I

ADMINISTRATION AND SCORING OF THE "CLINICAL" TESTS

(1) *The Hard Pin Pricking Tests*

The patient sat on a chair facing the tester, or lay on a couch for stimulation of the soles of the feet. He was told briefly what was about to happen, his arms were arranged in a position of extension and supination and he was asked to keep them in that position. The legs were arranged in a position of extension with the feet lying in a position midway between plantar and dorsiflexion. A pin held in the examiner's right hand was then made to pierce the skin of the palm or sole so that blood was drawn. This stimulus was repeated rapidly up to twelve times unless withdrawal of the part stimulated prevented this.

In Test 3, the protruded tongue was stimulated under the same conditions, the patient sitting up in a chair.

The "Low Grade" Defectives were all tested lying in bed.

(2) *The Soft Pin Pricking Tests*

These were identical to the hard pin pricking tests except that the pin pricking stimuli were not made to pierce the epidermis so that no blood was drawn.

(3) *Tickling Soles of the Feet*

The patient adopted the same position and was given similar instructions as for (1). A pin held in the examiner's right hand was made to pass from the heel forwards along the sole, and this was repeated up to twelve times.

(4) *Pressure to Tibiae*

The patient adopted the position and was given instructions as in (3) above. The examiner then placed his right hand upon the patient's leg just above the ankle, and transmitted his weight via his right hand on to the anterior border of the tibia. This stimulation was maintained for up to five seconds unless interrupted by the patient's reaction.

(5) *Pressure to Tendi Calcanei*

The patient, under the same conditions as (3) and (4) above, had his tendo calcaneus grasped between the right thumb and index finger of the examiner, who then squeezed maximally for a period of up to five seconds unless interrupted by the patient's reaction.

(6) *Pressure to the Supraorbital Regions*

The patient sat in a chair, was told briefly what was about to happen, and asked to maintain his position. The examiner then placed his right thumb on the area of the supraorbital nerve and pressed maximally for a period of up to five seconds unless interrupted by the patient's reaction.

(7) *Nasal Probes*

Under the conditions of (6) above, an orange stick held in the examiner's right hand was passed vertically upwards into the vestibule of the nose and pressed on maximally for a brief period of one to two seconds.

(8) *The "Clap" Tests*

The patient sat in a chair while the examiner stood behind him. Without warning the examiner suddenly clapped his hands loudly very near to the patient's ear.

(9) *The "Fist" Test*

The patient sat facing the examiner who suddenly and without warning lunged with his right fist towards the patient's open eye.

(10) *The "Match" Test*

Under the conditions of (9) above, the examiner suddenly lighted a match and approximated it quickly towards the patient's open eye.

(11) *Measurement of Test Responses*

This was done on a five point scale for each mode of response, i.e. movement withdrawal, facial wincing, and subjective experience.

(*a*) *Movement Withdrawal* (*M*)

0. No withdrawal of part stimulated.
1. Slight withdrawal of the part stimulated not sufficient to avoid further stimulus.
2. Moderate withdrawal almost sufficient to avoid further stimulation.
3. Marked withdrawal sufficient to avoid further stimulation.
4. Total withdrawal involving both the part stimulated and other parts of the body not being stimulated.

(*b*) *Facial Wincing* (*W*)

0. No facial wincing.
1. Slight rapid contraction of one area of facial musculature.
2. Slight rapid contraction of more than one area of facial musculature.
3. 1 plus vocal emission.
4. 2 plus vocal emission.

(*c*) *Subjective Experience* (*S*)

After each stimulus the patient was asked "did that hurt you" or "did that startle you"? If he replied in the negative, a score of 0 was made; if in the affirmative he was asked "would you say that hurt (or startled) you a little, moderately, or a lot". Depending upon his reply scores of 1, 2, or 3 were given. If the patient spontaneously related his experience as very painful or startling a score of 4 was given.

APPENDIX II

The Cold Pressor Test

The patient sat up to a table, and sphygmomanometer cuffs were applied to both arms. Oxymetric recordings were then made from the left hand and blood pressure recordings from the right arm. When basal recordings were obtained the right hand was immersed in a supersaturated solution of salt and ice with temperatures ranging between 2–5° C. This immersion was maintained for five minutes unless interrupted by the patient's reaction, and readings made every minute. The patient's hand upon removal was wrapped in a towel and minute readings made until basal levels were regained.

The Histamine Headache Test

The patient adopted the same position as for the C.P.T. After basal recordings had been made, 0·1 mg. histamine acid phosphate were injected into the right cubital vein. Recordings as for the C.P.T. were then made every minute until basal levels had been regained.

APPENDIX III

General Points Concerning Administration of the Tests

(1) The tests were carried out by the same examiners in a private room.
(2) Tests of the different batteries were always performed in the same order.
(3) The "clinico-physiological" battery of tests was always given within three days of the Clinical Battery.
(4) Retesting of a patient by the "clinical" and "clinico-physiological" Batteries was performed in all cases within three months.
(5) Patients who interrupted a battery of tests by refusal were very few in number and were allowed for in the analysis of the data.
(6) Tests 1 and 5 of the Clinical Battery were performed twice, first with the patient's eyes closed and secondly with them open and directed towards the part to be stimulated.

THE NATURE AND TREATMENT OF DELIRIUM TREMENS AND ALLIED CONDITIONS

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INTRODUCTION

DELIRIUM tremens and toxi-infective delirium are not now common diseases, but are still encountered often enough for their treatment to present problems. Delirium tremens is a medical emergency and intercurrent pneumonia is a serious complication, more likely to occur if the patient's over-activity persists. Toxi-infective delirium is less frequently accompanied by crude over-activity, but this may be a source of significant added strain in the severely ill patient, in whom it is more likely to occur. The standard treatment for delirium tremens is by sedation, and the giving of fluids and glucose. Paraldehyde seems to be the drug of choice. Opinion is divided on whether it is advisable to continue to give moderate amounts of alcohol. Sedation is the standard treatment in toxi-infective delirium, and here barbiturates tend to be used.

The role of intensive vitamin treatment in some toxi-organic states has been recently reported (1) and in a preliminary communication on the treatment of drug-induced mental disorder (1a), it was indicated that the technique of using massive doses of vitamins was first developed in connection with the treatment of delirium tremens. We treated our first case of this disorder by this means in 1944 and also at that time, arguing independently by the analogy between Korsakow's disease and pre-senile dementia mentioned by Strauss in 1946 (16), treated similarly a case of Alzheimer's disease. This latter case responded for three months with moderate improvement to 100 mg. aneurin hydrochloride intramuscularly daily combined with large doses of the crude B complex and ascorbic acid by mouth. Owing to various circumstantial factors at the time, treatment lapsed and the patient, a woman of 58, deteriorated. The response was not such as impressed us with the advisability of further experiment in the same dosage range, but, on the basis of later experience, we would now suggest more intensive parenteral treatment under in-patient conditions in the first instance.

The fourteen cases forming the material in which this paper is based comprise:

Alcoholic Deliria	5 cases
Deliria associated with alcohol and infection	2 cases
Deliria associated with infection	2 cases

Deliria associated with infection and sedation ..	2 cases
Non-delirious Alcoholic Psychoses	2 cases
Coma due to alcohol and barbiturates	1 case

They thus form a continuum with the cases of deliria, psychosis and coma due to drugs reported earlier (1).

The use of high potency vitamin mixtures was extended from delirium tremens to include deliria due to drugs, and toxi-infective delirium as well as certain other disorders of brain function on the grounds of—(1) the basic similarity of these toxi-organic reactions, (2) the probably similar biochemical aetiology, namely interference with brain carbohydrate respiration. The argument and the technique has been further extended to cover the milder mental reactions associated with and commonly accepted as part of the clinical syndrome of acute infections, and has been indicated elsewhere (1).

The premises from which this work started were simple: Delirium tremens was considered to be essentially an avitaminosis B_1 equivalent, but accepting the view that single avitaminosis did not typically occur clinically, we gave very large amounts of several vitamins. The decision with regard to oral and parenteral routes was at first in part determined by the availability of injectable preparations and the size of the dose by the acuteness of the clinical condition. Reference at that time to a small sample of the literature indicated the difference between our use of mixed vitamins and the usual method of giving one vitamin in high concentration and the technique has since been developed independently. The literature will be reviewed later, and a rationale for the method and an aetiological hypothesis for delirium tremens will be offered.

Case Reports

Case 1.—Male, aged 55, publican. On admission he was a case of typical delirium tremens with marked tremor and restlessness. He picked at the bedclothes and clutched at the air but was not violent. He was confused, incoherent, thick in speech and consciousness was moderately clouded. One day later he was more obviously hallucinated and talked of animals which he could see but of which he was not afraid. He was able to state his age, his residence and that he had always been nervous and in the habit of drinking four to five pints of beer daily.

Treatment was then begun, with a slow intravenous injection of 120 mgm. of aneurin hydrochloride and 600 mg. nicotinic acid. During the injection the patient's restlessness and confusion noticeably diminished and he was obviously quieter and more relaxed by the time the injection was completed, hallucinations and jactitations having disappeared. Tremor was also greatly reduced and he was able to sleep for an hour without sedation although previously paraldehyde had been quite ineffective as an hypnotic. In about four hours he commenced to deteriorate. Intravenous injection of 60 mg. B_1 and 600 mg. nicotinic acid was given three times daily for three days accompanied by 1,250 mg. ascorbic acid and large amounts of thiamin and nicotinic acid by mouth (see chart). Glucose was also included and on one occasion 3 gm. of sulphapyridine was injected as a precaution against the development of broncho-pneumonia. (Penicillin was not available at that time.)

On the following day he was still restless and confused. Tremor of the hands, a furred tongue and sluggish pupils were present but he was obviously better than on admission. Four days from the start of treatment he was mentally clear and much improved physically. Neurological signs had disappeared, he was no longer restless, and was sleeping well. Vitamins B and C continued to be given by mouth in large doses for a further three days. His discharge from hospital was held up by an irrelevant physical disability (hernia) for which he required surgical treatment.

Case 2.—Male, aged 19, seaman. Admitted "collapsed"—apparently in alcoholic stupor. On recovery of consciousness, he was apprehensive, restless, complaining and suspicious. Within a few hours it was clear that he experienced illusions and hallucinations—of men with green beards who were about to abduct him. (The theatre orderlies visiting the wards wore green gowns.) Within 24 hours he became difficult to manage, needed sedation, and attempted repeatedly to leave his bed to escape his imaginary tormentors. The past history included poor family relationships, repeated changes of job, sea-faring as an evasion of a difficult home situation, and heavy drinking when in port. The most recent bout of very mixed drinking had lasted ten days and for several days he had eaten little.

Examination revealed coarse tremor of hands, exaggerated knee jerks, relatively reduced ankle jerks, and tenderness on pressure of calf muscles. He was accessible for short periods though a poor witness and prone to wander from the point, as his attention rapidly reverted to his delirious experiences. He was given:

Vitamin B_1	400 mg. I.V.		four hourly
Vitamin C	300 mg.	per os	
Vitamin B_2	9 mg.		
Nicotinamide	50 mg.		
Multivite caps.	3		

During the first injection of aneurin he noticed no change, but within thirty minutes he found that the beards of the men had gone, and he could recognize them as ward orderlies. He remained tense and apprehensive but to a lesser degree. He slept for some time. After the second injection he became quite quiet, co-operative and well. A third injection was given. He was discharged 48 hours after the first injection.

Case. 3—Male, aged 64 years, publican. He had been a heavy drinker for many years and had a previous attack of delirium tremens some four months before admission. His condition on admission was typically one of delirium tremens, with visual hallucinations of a terrifying character and delusions that a gang of men had been raiding his house at night. He had been restless and sleepless for several days and showed some confusion and clouding of consciousness with gross recent amnesia. Physically he showed coarse tremor of the hands and face, the pupils were sluggish and there was arteriosclerosis. There were no signs of peripheral neuritis.

On the day of admission he was given thiamin 100 mg. I.M. and orally, 600 mg. nicotinic acid, together with 60 mg. each of thiamin, riboflavin and pyridoxin.

This was continued for three days after which the intramuscular thiamin was omitted. Ascorbic acid was not given. There was marked improvement within 24 hours of admission. He slept well after his first injection and his confusion and memory defect rapidly improved. Six days after admission he was cheerful and rational and this improvement was maintained, so that eight days after admission he was deemed to have recovered completely. He was, therefore, discharged at the end of seventeen days, when it was considered that he had reverted to his customary condition of chronic alcoholism with some facility and slight intellectual impairment.

Case 4.—Male, aged 42, bartender. The patient gave a history of dyspepsia and consistent heavy drinking (with no bouts of delirium), extending over the past ten years. In 1950 he uneventfully underwent gastrectomy for peptic ulcer after a month of preliminary medical treatment which included vitamin supplements to the hospital diet. No alcohol was given during his stay in hospital. In 1951, a year after operation, he was re-admitted on account of gross melaena due to anastomotic ulcer (Hb. 48 per cent.). During the interval his consumption of alcohol had remained steady. Four days after admission he commenced to be restless, getting out of bed, staring apprehensively at the wall, trembling, muttering to himself and approaching his food with suspicion. On questioning he admitted to visual hallucinations, involving queer animals and people hurrying to and fro, both on the wall and about the ward. In the succeeding twenty four hours he deteriorated. He was then given, intravenously:

Vitamin C	..	1,000 mg.
Vitamin B_1	..	1,000 mg.
Vitamin B_2	..	20 mg.
Nicotinamide	..	100 mg.

together with incidental sedation. Recovery was complete by the end of twenty four hours as far as psychotic experience and behaviour were concerned, although the patient remained emotionally labile for a further day.

This case shows some interesting features, namely that withdrawal of alcohol during the phase of medical treatment, when a nutritious diet and vitamin supplements were given, was not attended by any mental disturbance in spite of the history of consistent heavy drinking and dyspepsia. Similarly a high level gastrectomy was not followed by mental disturbance, and this may be correlated with the preceding month of medical treatment. (The stomach was shown to be the site of atrophic gastritis. At this time his haemoglobin was satisfactory.) Some ten months after operation, however, his general practitioner considered the patient to be developing an anxiety state and referred him for psychiatric opinion. His emergency admission in fact occurred two weeks before the arranged date of psychiatric interview. This was a year after operation and markedly reduced appetite had been present for a short time before the gross melaena occurred. Drinking had not apparently increased. On admission his haemoglobin was 48 per cent. and he was given two and a half pints of blood uneventfully. Some forty hours or so after this the psychosis became declared. In other words it would appear that the absence of even a poorly functioning stomach might have contributed to a biochemical disturbance of brain function presumably related to the reduced absorbtion of vitamins from food.

Case 5.—Male, aged 33, accustomed for many years to drinking five pints of beer a day had come to this country three months earlier on business. During his voyage of six weeks he had drunk more heavily and had come "near to delirium tremens" during the course of an infection at sea. For three weeks he had drunk excessively and eaten little. There was a history of depressive moods commencing during his preparation for the journey and becoming more marked as the months went by, from which he sought relief in alcohol.

When seen he presented a clinical picture of depression and of acute alcoholism. He was overflowing with shallow remorse and self-reproach. He beat his breast and cried out "No, no, don't!" particularly when he felt his moods of depression approach. He was tremulous, unsteady in gait, staccato in speech, staring in gaze, suspicious of his medical attendants, and while he did not admit to hallucinations, repeatedly glanced apprehensively over his shoulder. Confusion as such was absent, but he was unable to maintain a coherent conversation. Physical examination revealed discrepancies in the tendon jerks, which were uneven and unequal; mild lesions of the mouth, a smoothed tongue, faint cracks in the angles of the lips, and tenderness of the calf muscles to pressure. He was considered to be an acute alcoholic psychosis—illustrating incipient delirium tremens. He was given daily, intravenously:

Vitamin C	..	500 mg.
Vitamin B_1	..	500 mg.
Vitamin B_6	..	150 mg.
Nicotinamide	..	150 mg.
Pantothenic Acid		50 mg.

After the first injection his consumption of alcohol dropped. After two injections he was more composed. In a week he was well, but for some memory impairment and persisting depression. The depression responded to E.C.T. and he was sent home.

Case 6.—Male, aged 72. A long standing hypertensive (190/110) with arteriosclerosis, auricular fibrillation, emphysema, enlargement of the liver and pneumonitis, was admitted in a state of delirium. There was a past history of gross alcoholism and of an attack of delirium lasting eight days occurring thirty years earlier, during the course of a pneumonia. Evidence of recent increase in the amount of alcohol taken, and of secret drinking was available.

On examination there was tremor of the face muscles and the arms. He was restless, picking at the sheets and at the air for the butterflies he hallucinated. Disorientation was marked and he wrongly identified those around him on occasion. He repeatedly attempted to get out of bed and imagined that he was still engaged in his normal pursuits. When medication was offered, by mouth or by injection, he became annoyed and resistive. Auditory hallucinations were also present. He was given intravenously:

Vitamin C	..	400 mg.
Vitamin B_1	..	300 mg.
Vitamin B_2	..	20 mg.
Vitamin B_6	..	100 mg.
Nicotinamide	..	100 mg.
Dextrose ..	..	3 g.

During the administration he became steadily calmer and more lucid and by the end of the injection (some fifteen minutes) he was pleasantly co-operative, though the confusion had not cleared. The five assistants necessary at the start of the injection were no longer required to restrain him. The blood pressure dropped from 190/110 to 134/85 during the injection.

At intervals of eight hours he was given:

Vitamin C	..	200 mg.
Vitamin B_1	..	50 mg.
Vitamin B_2	..	5 mg.
Vitamin B_6	..	50 mg.
Nicotinamide	..	50 mg.
Dextrose ..	..	1·5 g.

The improvement however was not maintained and in fact he deteriorated to his original condition during the next thirty-six hours. He was then given the original dose, and this was repeated after a night's sleep. He at once fell asleep again and on waking sixteen hours later was quite well. There can be but little doubt that one of the factors in this patient's psychosis was the poor vascular supply to the brain. This case demonstrates the desirability of maintaining the high concentration of vitamins in order to obtain the best therapeutic result.

Indeed it is quite possible that his progress would have been more rapid had he been given the sort of dosage used in Cases 2, 4, 7, 10, but this was not done on account of his heart condition, as a reduction of blood pressure had occasionally been noticed in other patients receiving large amounts of vitamins intravenously. The delirium in this case commenced within the first thirty-six hours of the infection, about eighteen hours before admission and there is no reason to believe that his intake of alcohol had been altered before the infection supervened.

Case 7.—Female, aged 42, was admitted on account of a compound fracture of the right tibia and fibula. She walked on her fractured leg to the hospital accompanied by her husband, both in a drunken state. Evidence indicated a long standing heavy consumption of spirits.

The fracture was set and plastered under thiopentone, nitrous oxide, oxygen and ether, the patient having become sober. Pyrexia 99°–100° F. was present and persisted, as did the raised pulse and respiration rates (X-ray five days later showed bilateral pneumonitis), and did not respond to penicillin 2,000,000 units daily for two days, followed by 600,000 units daily. Two days after admission she suddenly became acutely hallucinated, restless and voluble. She imagined men to be walking outside her window and rapidly became hostile, fearful and accused the house-surgeon of murdering and dismembering her husband, even though a few minutes later she would carry on a conversation with her spouse whom she declared to be under the bed or in the corridor. Her restlessness and noisiness increased steadily and she became quite unco-operative. Sedatives had little or no effect. On the third day of the delirium she was given, intravenously:

Vitamin C	..	1,500 mg.
Vitamin B_1	..	1,000 mg.
Vitamin B_6	..	200 mg.
Nicotinamide	..	200 mg.
Dextrose ..	..	3·5 g.

with considerable improvement for several hours. Instructions for repeated doses of half the above amounts at 4–8 hourly intervals miscarried and only one injection of the halved quantities was given in the next twenty hours. She remained, however, less disturbed.

A further half dose was given with little apparent immediate benefit but after a sleep the patient was quite normal and remained so. This case shows, as does Case 6, the desirability of maintaining a high concentration of vitamins. It would appear, however, that much larger doses seem to be required when both infective and pharmacological factors (alcohol or drugs) are associated with the delirium than when the infective state alone appears responsible for the mental disturbance (1).

Case 8.—Female, aged 32, jilted by her lover two days earlier, and much distressed thereby, presented with pain in the right chest and mild mental confusion of some ten to twelve hours' duration, but increasing in intensity. When seen in bed three hours later, she was passively resistant to nursing attention and medical examination. She lay on her right side, moaning, inattentive to surroundings, and when induced to answer questions, her replies though relevant, lacked normal courtesy. Disorientation was absent but she could not sustain a train of thought or give consistent attention. Physical examination revealed no localizing signs at this stage but the degree of "toxaemia" was so pronounced that fulminating influenza was considered the most likely diagnosis. T. 103° F, P. 128, R. 28.

The past history included concussion nine months earlier and glandular fever (treated with streptomycin) four to five months before the present illness. The patient had a labile low blood pressure. She was given intravenously:

Vitamin C	..	400 mg.
Vitamin B_1	..	300 mg.
Vitamin B_6	..	50 mg.
Nicotinamide	..	100 mg.

One hour later she was mentally clear and co-operative. The following morning pain in the right shoulder was present and the right lower lobe was solid. Penicillin 1,000,000 units was given. The patient remained clear-headed, cheerful and experienced no sense of illness. T. 101° F., P. 90, R. 30. Further doses of intravenous vitamins were given daily for ten successive days:

Vitamin C	..	300 mg.
Vitamin B_1	..	50 mg.
Vitamin B_6	..	50 mg.
Nicotinamide	..	50 mg.
Pantothenic Acid		25 mg.

Penicillin being continued at 600,000 units in the day. Recovery was uneventful and she set herself to put her emotional affairs in order.

This case demonstrates the response of the mental obfuscation which here was not sufficiently marked to be called confusional psychosis, to intravenous vitamins while the disease process continues (1). This case (lacking a history of alcoholism) could well be contrasted with Case 7 where the persisting infection and the past history of gross alcoholism was associated with a psychotic behaviour more resistant to vitamin therapy. The smaller doses were used in this case as it had been found that these are more suitable to the milder toxic features accompanying acute infections (1).

Case 9.—Male, aged 69 years with no occupation, was admitted under certificate. Five and thirteen years earlier he had experienced depressive episodes for which he had been admitted to hospital and from which he recovered well.

On this occasion his mental state was one of toxic confusional psychosis associated with pneumonia. He was confused and showed clouding of consciousness. Disorientation in time was present. He had vague paranoidal ideas that he was being poisoned and he was restless noisy and frequently violent. Physically he was regarded as dangerously ill on admission, owing to his chest condition which included areas of consolidation in both lungs and many moist sounds at both apices.

On the day after admission he was given intramuscular injections of aneurin hydrochloride 75 mg. plus nicotinic acid 100 mg. q.t.d. plus ascorbic acid 300 mg. orally t.i.d. This regime was continued for forty-eight hours. Sulphonamides were also given. By the following day he was significantly better, and a week later he had greatly improved mentally and physically: although still feeble, he was by then regarded as out of danger.

Treatment was continued by benzedrine and sedation and improvement was steady until he left hospital, recovered nine weeks after admission.

Case 10.—A female, aged 22, a nurse, suffered from severe pain in the lower limb associated with a small localized undirected mass in the deep tissues of the posterior part of the thigh. A low grade pyrexia was present, T. 99–99·6° F. For the pain she received pethidine 200 mg. or more daily. After several weeks, during which no adequate diagnosis could be established, it was noticed that her composure was becoming undermined and her behaviour more emotional and over-reactive. She was then transferred to another hospital on admission to which she was noticed to exhibit "choreiform" movements, particularly of the upper limbs. For the control of these she was given, in forty-eight hours, the following—Phenobarbitone 19 gr., Pethidine 400 mg., Sodium Amytal 6 gr. When seen by one of us she was accessible only momentarily. She lay in bed repeatedly throwing herself about and contorting her body, moaning, clamouring for relief of pain, she was childish at times, and slurred in speech. Occasionally she bewailed her removal from the care of the doctor who previously attended her, bleating "He doesn't want me any more" and at these times would beat her head violently against the pillows. Some of her infrequent responses to remarks suggested a Ganser syndrome. For instance when it was suggested that she should switch off the light which offended her eyes, she searched everywhere in a clumsy manner but succeeded in avoiding the switch which was obvious, handy, and whose position in the side room she must have known very well indeed from her work on the ward.

She was given intravenously:

Vitamin C ..	1,500 mg.
Vitamin B_1 ..	1,000 mg.
Vitamin B_2 ..	10 mg.
Vitamin B_6 ..	100 mg.
Nicotinamide ..	200 mg.
Pantothenic Acid	25 mg.

This served to make her far less restless and in the next twenty-four hours she needed only 200 mg. of pethidine for the pain and no sedation at all. Twenty-four hours later the same amount was repeated. She slept and was quite recovered, psychiatrically, when she woke in the morning. The pain, swelling and pyrexia continued.

This case is regarded as illustrating a combination of drug-induced and toxi-infective psychosis. In the absence of pyrexia one would have expected the patient to be fairly deeply narcotized in view of the intensity of the sedation.

Case 11.—A woman of 33, a markedly neurotic subject, received E.C.T. with anaesthesia and muscle relaxants for a depression of some three years' standing after failing to respond to acetylcholine therapy. The course of electroplexy was attended by increasing disinhibition of behaviour and the emergence of some early mild hypomanic reactions. The last (10th) treatment was given at a time when the patient had been pyrexial for two days. Pyrexia lasted another thirty-six hours and at one point reached 102° F. (influenzal coryza was diagnosed). Anorexia had been marked for some months and there had been a loss of one stone in weight. A day after the last electrical treatment she became acutely psychotic and was first seen by one of us in this state a day later. The clinical picture was mixed. Psychomotor over-activity with rapid change of mental content involving several themes and emotional lability (the mood changing from tearfulness to elation and irritability) were presenting features. Clouding of mind was present with poor accessibility to rational conversation. She was acutely fearful of being taken away from home and much pre-occupied with emotionally significant themes such as her own integrity and her husband's (? imagined) infidelity. The tongue was dirty and raw, the calves tender and the tendon jerks uneven. She was given intravenously:

Vitamin C ..	750 mg.
Vitamin B_1 ..	500 mg.
Vitamin B_2 ..	20 mg.
Vitamin B_6 ..	100 mg.
Nicotinamide ..	200 mg.
Pantothenic Acid	10 mg.

in the day for five days with the result that a much more manageable simple hypomania was left after three days treatment.

Case 12.—A man, aged 73, was seen on account of increasing confusion of recent onset. The history showed that for many years he had drunk one and a half bottles of whisky per day, with no overt ill effects, but that in the last eighteen months this had been reduced to about one bottle per day. Sixteen months earlier he had been given colchicine for a rash encircling the neck and soon after this he had developed a slight coronary infarct, from which he had recovered uneventfully. Nine days before being seen he had vomited and commenced to talk gibberish. His secretary noticed that one side of his face was immobile. For the next week he was treated by rest in hospital, the condition being regarded as a mild stroke, but he did not improve and was then permitted to return home. The night before being seen he had a temperature of 102° F.

On examination he looked ill, T. 99·4° F., P. 98, R. 24. He was obese, emphysematous and there were signs of early pneumonia at the lung bases. Psychiatrically, he was completely confused with gross impairment of memory, even over a two-minute period. The right angle of the mouth drooped and the right knee jerk was absent. No other neurological signs were elicitable. The impression was gained that the absent right knee jerk was a long standing sign, unconnected with the present condition. The blood pressure was 110/70. Signs of vitamin insufficiency (1) included: smoothing of several areas of the tongue, minor lesions of the inner surface of the lower lip, dryness and scaling of the limbs, marked tenderness of the calf muscles on pressure.

He was given intravenously:

Vitamin C	500 mg.
Vitamin B_1	200 mg.
Vitamin B_2	10 mg.
Vitamin B_6	200 mg.
Nicotinamide	200 mg.
Pantothenic Acid	12½ mg.
Dextrose	1 g.

at 2 p.m. By 4 p.m. he was considerably more alert though bouts of confusion persisted. By 11 p.m. he had deteriorated and the injection was repeated. Overnight he slept fitfully until 2 a.m. and was then given sodium amytal 3 gr. which was followed by slumber. On waking further mental improvement was apparent, but the signs of consolidation at the bases had progressed, and he remained pyrexial. The same dose of vitamins was given once in the next day and penicillin commenced at night. By evening his confused state was very considerably reduced, occurring only for a few minutes at a time. Parenteral vitamins were continued for several more days, the psychiatric syndrome resolving rapidly.

It is a matter of speculation whether the initial mental disturbance might have been a variant of Wernicke's encephalopathy, as opposed to a slight thrombosis or haemorrhage.

Case 13.—A 48 year old male was prone to bouts of excessive drinking which would last up to nine days. At these times he ate little and would drink one to two bottles of whisky per day. In two of these bouts he was treated with vitamins parenterally. On the first occasion he had been drinking for six days and was given:

Thiamin	200 mg. I.M. q.t.d.	
Ascorbic Acid	300 mg.	orally q.t.d.
Riboflavin	6 mg.	
Nicotinamide	50 mg.	

After one day he left the nursing home against advice to resume his drinking but returned two days later when he was given:

Ascorbic Acid	1·5 g.	intravenously.
Thiamin	1·0 g.	
Riboflavin	10 mg.	
Pyridoxin	100 mg.	
Nicotinamide	200 mg.	
Glucose	1·0 g.	

Two hours later he was composed and co-operative. Half the above dose was given at half-day intervals on three occasions and the patient was discharged. On the second occasion he presented after drinking for seven days. He was given the larger dose mentioned above, but for the fact that instead of including B_6, 100 mg. in the mixture, Pyridoxin 400 mg. was injected twenty-five minutes before the rest (in view of Wordsworth's interesting observations on the relief in three minutes of simple drunkenness by 100 mg. of vitamin B_6 intravenously (40)) but without apparent effect. His composure was restored forty-five minutes after the injection of the mixed vitamins was completed. Three further injections at half day intervals were given.

The failure of pyridoxin alone to influence the clinical picture in this case is not surprising, as simple drunkenness and alcoholic psychoses very probably differ greatly in their biochemical nature. The clinical picture presented by this patient before treatment with parenteral vitamins included tremor of face and hands, slurring of speech, unsteadiness of stance, retardation, truculence and suspiciousness to the point of near-delusion (he feared his food might be tampered with and could not be persuaded to eat it until a while after he had received the injection).

This case illustrates the advantage of the large dose and the parenteral route, particularly when quick results are necessary.

Case 14.—Barbiturates and Alcohol.—The synergistic effects of barbiturates and alcohol have a topical significance and the following case is described as it connects the material of this paper with some other aspects of the use of parenteral high potency vitamin mixtures described elsewhere (1, 1a).

Miss G.B., aged 29, lived alone in a small flat. She lacked appetite and slept badly. Depressive mood swings, lasting up to three weeks, had occurred frequently since adolescence. For some months she had been more severely and persistently depressed following an emotional upset. For forty-eight hours she neither slept nor ate. She then consumed 2/3 of a bottle of whisky and 21 gr. of Sodium Amytal. A friend chanced to call at this point and hurried the patient to a nearby doctor, on whose surgery floor she went into coma. She was at once transferred to a nursing home, receiving 6 mg. picrotoxin en route. On arrival she was given:

Vitamin C ..	1,500 mg.	intravenously.
Vitamin B_1 ..	1,000 mg.	
Vitamin B_6 ..	100 mg.	
Nicotinamide ..	200 mg.	
Dextrose	2 gm.	

Three hours later she was awake, oriented and rational, though tense. Within four hours she was eating poached eggs on toast.

COMMENT ON DOSAGE

In Table I the doses used in the various cases are shown. It will be noticed that the doses vary from case to case. The really rapid improvements or recoveries tend to be associated with the dosage pattern—Ascorbic acid 1,500 mg., aneurin hydrochloride 1,000 mg., nicotinamide 100–200 mg. The fairly frequent inclusion of pyridoxin, riboflavin and pantothenic acid has not so far led to obvious differences in response of the cases who receive them —although there is evidence that pantothenic acid may offset the hypotensive response sometimes associated with large doses of aneurin hydrochloride (1). Case 8 is an exception to the rule that strikingly rapid improvement is associated only with the massive doses. In this patient, however, there was no evidence that alcohol or drugs were implicated in the toxi-confusional mental state, and her response to the lower dosage is in keeping with findings in other conditions dependent upon infection, and not associated with clinical psychosis which will be published elsewhere.

In attempting to evaluate the technique of intensive mixed parenteral vitamin treatment of deliria associated with alcohol and toxi-infective states certain limitations must be kept in mind:

(1) The amount of alcohol consumed is usually unknown except in roughest measure. The onset of delirium tremens and/or psychosis may however be regarded as indicating a critical level of physiological disturbance and hence providing a common base line.

(2) The dosage pattern and its results:

(*a*) The pattern was empirical.

(*b*) Physiological considerations led us to include B_2, B_6 and pantothenic acid, but so far no striking evidence as to their short term importance has been obtained (e.g. in Case 13, the clinical result was the same whether 100 mg. or 400 mg. of B_6 was used).

(*c*) The dosage pattern has varied, even in its two most significant factors —vitamins C and B_1—though nicotinamide when used has varied less, between 100–200 mg.

(*d*) All the rapid responses have been associated with vitamin C 900 mg.–1,500 mg., B_1 1,000–1,200 mg., nicotinamide 100–200 mg. with the exception of Case 8 where the psychosis was in no way associated with drugs or alcohol, but only with infection (1).

Case	Age/Sex	Diagnosis	Duration before Vitamins	Past History of Alcoholism	Days of Vitamin Therapy	Dextrose	Ascorbic Acid C.	Aneurin HCL. B_1	Nicotinic Acid	Nicotinamide	Pyridoxin B_6	Riboflavin B_2	Pantothenic Acid	
(1)	55/M	D.T.s	2 days	++++	3		1,250 mg. oral	180 mg. I.V. 75 mg. oral +(60 mg. B_1 in 1st injection)	1,800 mg. I.V. 600 mg. oral					I.V. given in 3 aliquots per day. Immediate improvement.
(2)	19/M	D.T.s	1 day	++	1		900 mg. oral	1,200 mg. I.V.		150 mg. oral		27 mg. oral		Symptom free in 18 hours. B_1 given in 3 aliquots at 4 hourly intervals
(3)	64/M	D.T.s	several days	++++	7		0	60 mg. oral 100 mg. I.M.	600 mg. oral	Multivite caps. three, 4 hourly 200 mg. oral	60 mg. oral	60 mg. oral		Improvement in 24 hours. Symptom free in 6 days.
(4)	42/M	D.T.s	1 day	++++	1		1,000 mg. I.V.	1,000 mg. I.V.		100 mg. I.V.		20 mg. I.V.		Recovery within 24 hours. Improvement ++ in few hours.
(5)	33/M	D.T.s incipient	several weeks	+++	5		500 mg. I.V.	500 mg. I.V.		150 mg. I.V.			50 mg. I.V.	Improvement in a few hours. Recovery within a week.
(6)	72/M	Alcoholic Delirium with infection	1 day	++++	2	3 g.	400 mg. I.V.	300 mg. I.V.		100 mg. I.V.	100 mg. I.V.	20 mg. I.V.		Repeated (after intermediate smaller dosage) after 36 hours and again 8 hours later—Recovery.
(7)	42/F	Alcoholic Delirium with infection	3 days	++++	1	3 g.	1,500 mg. I.V.	1,000 mg. I.V.		200 mg. I.V.	200 mg. I.V.			Two half doses given in the following 24 hours. Recovery in 36 hours.
(8)	32/F	Delirium with infection	15 hours	Bouts of social drinking	10	1 g.	400 mg. I.V.	300 mg. I.V.		100 mg. I.V.	50 mg. I.V.			Mental symptoms clear in one hour.
(9)	69/M	Delirium with infection	several days	—	2	—	900 mg. oral	300 mg. I.M.	600 mg. I.M.					Mentally improved in 3 days, clear in one week.
(10)	22/F	Delirium with infection and sedation	2 days	—	1	3 g.	1,500 mg. I.V.	1,000 mg. I.V.		200 mg. I.V.	100 mg. I.V.	10 mg. I.V.	25 mg. I.V.	Repeat once (24 hours later). Mentally clear 12 hours after 2nd injection (i.e. in 36 hours).
(11)	33/F	Delirium with infection and sedation	2 days	—	5	—	750 mg. I.V.	500 mg. I.V.		200 mg. I.V.	100 mg. I.V.	10 mg. I.V.	10 mg. I.V.	In two aliquots given daily confusional aspects clear in three days.
(12)	73/M	Non-delirious alcoholic psychosis	9 days	++++	5	2 g.	1,000 mg. I.V.	400 mg. I.V.		400 mg. I.V.	400 mg. I.V.	20 mg. I.V.	25 mg. I.V.	In two aliquots at 8 hourly intervals, initial transient improvement in 2 hours, considerable improvement in 36 hours.
(13)	48/M	Non-delirious alcoholic psychosis	7 days	++++ in bouts	2	2 g.	1,500 mg. I.V.	1,000 mg. I.V.		200 mg. I.V.	100 mg. I.V.	10 mg. I.V.		Half doses repeated b.d.—3 injections. Recovery in an hour.
(14)	29/F	Alcoholic and barbiturate coma	1 hour	Social drinking	1 injection	2 g.	1,500 mg. I.V.	1,000 mg. I.V.		200 mg. I.V.	100 mg. I.V.			Awake in 3 hours. Eating in 4 hours.

(3) In order adequately to establish the most satisfactory pattern of dosage, it would be necessary to have a much larger series of cases, and to work with the theory of limiting factors. Of all the vitamins to be used, only one should be in less than saturation concentration. Thus the clinical effects of varying the dose of one factor could be assessed. In order to apply this method and have sufficient results for statistical analysis, series as large as those published by Rosenbaum, Petrie and Lederer (10) are probably necessary, but instead of supplying, as did those authors, a single vitamin in the context of almost certain relative insufficiency of the others (and thus inviting further biochemical imbalance), it would be necessary to saturate with all factors except the one under observation. Even so the results are not likely to be simple and easy for analytical purposes, because it is known, for instance in the case of pantothenic acid and riboflavin, that the administration of one causes a rise in the blood level of both (41).

LITERATURE

During the period 1937–43 a good deal was written concerning the value of different vitamins, usually thiamin or nicotinic acid, in various psychiatric conditions, particularly delirium tremens. Both thiamin (2, 5, 6), and nicotinic acid (3, 4, 7), had advocates and critics as specific "cures" in delirium tremens while it was also claimed that the administration of either was ineffective (10, 11). Other workers (8a, b, 9a, b) reaffirmed the good results of treatment without the specific use of vitamins although much ascorbic acid was apparently included in their regime. The administration of vitamins as prophylaxis against the central and peripheral neural sequelae of alcoholic psychoses was advocated by some (18a, b, c) who opposed their use in the treatment of the acute condition. These workers also cited instances where recovery from delirium tremens did not occur until large injections of vitamins and/or liver were given, and they admit freely that the early differentiation of cases needing vitamins from those who would recover without their aid was not possible.

Thiamin given parenterally was reported as of value in the treatment of Korsakow's psychosis and alcoholic psychoses other than delirium tremens (13, 14, 15) and also in presenile dementia (16). Some workers stressed the fact that the mode of action was obscure, as Avitaminosis B_1 could not be demonstrated in Korsakow's disease (15, 12a).

The value of nicotinic acid in certain psychoses was also established in this period. Alcoholic pellagra was identified with true pellagra (17, 30) and later acute nicotinic acid deficiency encephalopathy was described, initially in alcoholics (18, 19). This syndrome includes stupor, cogwheel rigidities and grasping and sucking reflexes. The case often showed signs of mixed vitamin lack as well as organic disease. Meanwhile the value of nicotinic acid in the pellagrous psychoses had been shown (20a) and was then extended to cases of stupor with evidence of nicotinic acid lack short of typical pellagra. Later nicotinic acid was demonstrated to be effective in some instances of clouded consciousness, not showing signs of pellagra, but conforming to the picture of toxi-exhaustive psychosis (20b, c).

This material demonstrates a nexus comprising vitamins, alcoholic psychoses and their sequelae, pellagrous psychoses and certain "organic" psychoses not usually considered as avitaminotic in nature. Concepts of avitaminosis and deficiency diseases influenced clinical thinking and gave rise to therapeutic attempts centred on the discovery of a single vitamin which would cure all instances of the same clinical syndrome. In 1943 Sydenstricker (20c) observed that Wernicke's encephalopathy, which was known to respond very well indeed to thiamin, responded even better to six intravenous injections per day of 50 mg. nicotinamide and 5 mg. each of thiamin, riboflavin, pyridoxin and calcium pantothenate. This dosage is of interest in that the mixture and the amounts are unusual for the time, and but for the absence of vitamin C the daily totals approach those we have used, although it was not until recently that Sydenstricker's paper came to hand.

The general trend in this earlier literature was to give thiamin, commonly by injection, in daily doses of 10–20 mg. occasionally 50 mg. and rarely 100 mg. nicotinic acid was given, usually orally, in amounts up to 2,000 mg. in the day in the treatment of acute nicotinic acid deficiency encephalopathy. Nicotinamide was given in 1/3 the amounts of the acid. Those vitamins not given specifically were supplied in generous dietary amounts. Some of the case reports (3, 18, 20a) reveal that another vitamin had been given in specific fashion before the one claimed as the cure, but that the possibility of integration of effects was overlooked. Mainzer and Kraus (3) gave 550 mg. of thiamin in two days to a patient who, from their account exhibited evidence of mixed vitamin lack while suffering from delirium tremens. His condition worsened, but responded when 100 mg. and 500 mg. of nicotinic acid was administered in the subsequent two days. Mainzer and Kraus consider that nicotinic acid was the specific therapeutic agent. Rosenbaum, Piker and Lederer (10) analysing the results of the use of thiamin and of nicotinic acid in a large number of cases of delirium tremens, and comparing these cases with others treated by conventional methods point out that there is no marked difference in duration of psychosis although those patients receiving thiamin (50 mg. daily) required much less sedative than any other group. Those receiving nicotinic acid required, according to the figures given, more sedatives than any other group, but this feature is not commented upon by the authors. Sydenstricker *et al.* (20a) present nine case histories to illustrate the value of nicotinic acid, and in no less than five of these significant amounts of liver and/or thiamin were also given parenterally.

More recent work in these fields exploits high intravenous dosage of vitamins. Sydenstricker (20b) had reported a case of acute psychosis in a pellagrin controlled by 600 mg. nicotinic acid and other vitamins orally daily for a month. The psychosis responded in fifteen minutes to the intravenous injection of 150 mg. sodium nicotinate. Seliger (21) recorded the use of 500–600 mg. Thiamin given intravenously in a glucose drip, together with general sedation, as a method of treating delirium tremens with symptomatic recovery in ten hours, and Fischbach (22) claimed 25 mg. of A.C.T.H. to be specific in delirium tremens although he failed to consider the influence of the three litres of glucose solution containing 1,000 mg. of ascorbic acid which were also given. Toxi-confusional psychoses associated with laboratory findings indicative of liver failure were treated successfully with nicotinamide 300 mg. intravenously daily and later 100 mg. orally daily, provided perseverance up to four months was shown (23). A high vitamin diet was part of the regime.

Apart from Sydenstricker's (20c) remarks about Wernicke's encephalopathy, the work reviewed shows the tendency to exhibit one vitamin in high concentration in acute psychoses, and to assume that dietary measures will suffice for the rest. It was accepted that spontaneously occurring vitamin lack rarely, if ever, involves only one factor, and it was known that the administration of a single vitamin in high concentration may precipitate signs of deficiency of other vitamins, particularly among the inter-related members of the B group (24).

Such mechanisms may indeed account for the occasional report of evidence (3, 10) that large amounts of a given vitamin have been followed by deterioration of the clinical condition.

Some confusion of thought appears to have developed in the literature on vitamins and psychosis. The clinical search has been for the single effective cause of the given clinical syndrome analogous to the role of the pneumococcus in pneumonia. This is an example of the mechanical causality recently examined critically by Strauss (25), Bomford (26) and Sir Russell Brain (27) and of the undue extension of concepts beyond their context discussed by Pirie (28). The idea of the single effective cause in this field contradicts the known inter-relationship of the B vitamins and this was partially reconciled by the method of dietary supplementation. Finally the view of vitamins as simple catalysts in tissue metabolism, daily requirements of which are small, was at variance with the use of the larger therapeutic doses. Nicotinic acid requirements may be an exception here for these are not strictly determined. These latter considerations led to speculation on the drug-like actions of the vitamins when given in large amounts (29a), particularly with regard to nicotinic acid and vasodilation, but this view has been met by the evidence that the amide is as effective, even though lacking the vasodilatory activity of the acid (29b).

So far, the use of vitamins in certain major psychoses and their organic sequelae have been described, and two methods are discernible.

(1) The specific exhibition of a single vitamin—the value of this technique being much challenged especially with regard to delirium tremens.

(2) The use of moderate amounts of mixed vitamins in the treatment of certain organic conditions. Here while the therapeutic value was more readily admitted, the aetiological justification was much doubted, as avitaminosis was deemed absent in these states.

Let us now turn to certain clinical and physiological considerations, which are considered to have a bearing on the nature and treatment of delirium tremens and certain toxic confusional psychoses.

CLINICO-PHYSIOLOGICAL CONSIDERATIONS

Delirium tremens is always associated with alcohol, but may persist in the absence of alcohol from the C.S.F. (35). The onset is often preceded by three days or so of over-activity associated with abstention from alcohol as well as food. Delirium tremens, however, does not occur if adequate food intake and dietary excess of vitamins is ensured (36). This evidence may be held to show that delirium tremens is not simply caused by the presence of excessive amounts of alcohol in the tissues. Drunkenness, narcosis or anaesthesia occur in such conditions. Factors precipitating delirium tremens include pyrexia, infection, anaesthetics, operation, injury, exposure and vigorous exercise. These situations of stress like the prodromal over-activity make heavy demands on the vitamin B and C supplies of the body (37, 31, 32).

Pathological indulgence in alcohol is associated with impaired intake and absorbtion of carbohydrates and vitamins, and lack of ascorbic and nicotinic acids and of thiamin has been demonstrated (12a, b, c). (The implications of vitamin insufficiency for the stability of brain carbohydrate respiration, and the crucial role of vitamins in the structure of the brain enzymes has been discussed elsewhere (1, 1a).) Thus the carbohydrate respiration of brain tissue, in which vitamins are essential, is put under stress. Alcohol can spare carbohydrate and protein in general metabolism, but only to a limited extent. In brain respiration, alcohol produces an alteration of the metabolic pattern as shown by the reduction both of the oxygen uptake and the R.Q. (38a, b, 33a, b). Two concurrent processes may thus be postulated in the development of delirium tremens:

(1) A progressive imperilling of the basic carbohydrate respiration of the brain due to increasing insufficiency of vitamins. The mild but increasing hyperglycaemia in delirium tremens is consistent with this suggestion (39a, b, c).

(2) A deviant pattern of metabolism due to the forcing of alcohol as an alternative oxidizable substratum.

Anorexia, a prodromal feature of delirium tremens occurs also as a result of thiamin lack. Whatever the origin, the abstention from food may be considered to precipitate or aggravate matters, for supplies of carbohydrates and vitamins as well as alcohol are cut off. The prodromal over-activity, itself a product of the deteriorating cerebral metabolic state makes further demands on the inadequate vitamin stores.

The psychosis may be deemed to declare itself when the chain of reversible oxidization-reduction reactions characteristic of intracellular brain carbohydrate metabolism (34) is sufficiently impaired. Perhaps the special clinical features of delirium tremens are in part determined by the deviant pattern of metabolism due to the alcohol. The basic structure of the delirium, however, is similar to other pharmacologically determined disorders (1) where alcohol is not implicated, and favours the opinion that the essential disturbance is one of disordered brain carbohydrate respiration and acute vitamin insufficiency.

If this interpretation of delirium tremens be accepted (imperilling of carbohydrate respiration due to vitamin lack and forcing of alcohol as an alternative substratum with consequent alteration of metabolic pattern), then it follows that in different cases, different factors may predominate. This reconciles the earlier conflicting evidence on the therapeutic value of glucose, fluid, thiamin and nicotinic acid and suggests that treatment should provide all relevant factors. Vitamins should be given in amounts not only large enough to cover the likelihood of therapeutically induced imbalance, or daily dietary needs, but large enough to rectify the disturbed metabolic pattern of the brain, were this to be due to lack of one or several components of the therapeutic barrage.

The patterns of dosage employed in our cases is in keeping with this general theme and, although the number of cases is small, suggests that the more rapid results are obtained with the higher total daily doses of vitamins. We would suggest that further clinical trial is called for and that in a typical delirium tremens or toxi-infective delirium—the following dosage regime be used:

Ascorbic acid 1,500 mg., aneurin hydrochloride 1,000 mg., nicotinamide 100–400 mg., pyridoxin 200 mg.; repeat in 4–8 hours s.o.s., followed by half doses at 4–8 hourly intervals as indicated clinically.

Elsewhere (1) it has been pointed out that the bodily reserves of ascorbic acid, thiamin and nicotinamide are relatively meagre if sudden demands have to be met, and that the bodily requirements of these vitamins are raised by infection, increase of metabolism, and increase of temperature. It has also been shown that barbiturates exert their action in the central nervous system by interfering with the respiratory enzymes of the brain (33a, b) and thus the combination of barbiturates and enzymes may be clinically reversed by the administration of vitamins, or the formation of new enzymes may be thus facilitated. This it is suggested is the way in which the vitamins act in the drug induced psychosis (1). That toxic-delirium is probably due to vitamin insufficiency has also been discussed (1). That the synergistic effect of alcohol and barbiturates impinges on the enzyme systems of the brain is consistent with the dramatic results obtained in Case 14.

Summary

Fourteen cases of delirium and allied psychotic states associated with alcohol, infection and at times drugs, have been treated with high potency vitamin mixtures given parenterally.

The response obtained is sufficiently good to warrant more extended trial, and a pattern of dosage for this is suggested. The technique, which was developed empirically, can be shown to be supported by physiological considerations.

Delirium tremens may be considered as resulting from the imperilling of the basic carbohydrate respiration of the brain (due to vitamin insufficiency) coupled with the forcing of alcohol as an alternative oxidizable substrate, resulting in deviant patterns of brain metabolism which become manifest as the psychosis.

Acknowledgments

We acknowledge with pleasure our indebtedness to Dr. B. S. Cooper, for the clinical history given as Case 8.

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THE ROLE OF NICOTINIC ACID (NIACIN) IN MENTAL HEALTH AND DISEASE

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SECTION A: THE AETIOLOGY AND PSYCHIATRIC MANIFESTATIONS OF PELLAGRA

1. INTRODUCTION:

THE VITAMIN B COMPLEX AND THE AETIOLOGY OF PELLAGRA

SHORTLY before the end of the last century, Eijkman observed that fowl receiving a diet of polished rice developed a disease which he believed to be of the same nature as human beri-beri. It was subsequently shown that this condition in fowl (polyneuritis gallinarum), and beri-beri in man, could both be cured by the addition to the diet of rice polishings or an extract prepared from them. In 1911, Funk obtained from rice polishings a crystalline substance capable of preventing or curing beri-beri, which he named "vitamine" in view of its evident importance to life, and in the erroneous belief that it had the chemical structure of an amine. Four years later, McCollum and Davis demonstrated that at least two such dietary factors were necessary for growth in rats—"fat-soluble A" and "water-soluble B". Before long it was recognized that the latter factor had the properties of the antineuritic "vitamine", and a number of similar organic compounds were discovered, which were essential constituents of the diet in minute quantities, and for which the general term "vitamin" was agreed upon. For several years it was assumed that water-soluble vitamin B (contained in yeast, rice polish, liver, etc.) was a single entity, but in 1919 Mitchell noted that certain vegetables rich in the antineuritic principle had little power to promote growth, and in 1926 two fractions were distinguished, each essential for growth—thermolabile vitamin B_1, containing the antineuritic principle (thiamin), and thermostable vitamin B_2.

Now a disease known to the peasants of Lombardy as pellagra (from "pelle agra", meaning rough skin) was first recorded in medical literature by the Italian physician Frapolli in 1771. A Spaniard by the name of Casal had described this condition some years earlier under the term "mal de la rosa", and had attributed it to a poor diet, but it was not until 1915 that its dietary origin was conclusively demonstrated by Goldberger. At that time, pellagra was considered due to the "biological inferiority" of protein consumed (causing deficiency of essential amino-acids) and it was another ten years before it was shown to result from vitamin deficiency (as originally predicted by Funk). Not long after the latter discovery, it was postulated (1) that the pellagra-preventive factor was a single substance, vitamin B_2 (G), the thermostable fraction of the vitamin B complex, but in 1933 riboflavin was isolated, and other factors were subsequently separated from the vitamin B_2 complex, one of which was nicotinic acid (niacin).

Nicotinic acid was first derived from nicotine by the chemist Huber in

1867, and Funk (2) reported its presence in his extracts in 1911, but its physiological significance was still not apparent at that time. Some years later, Warburg (3) recognized its association with tissue respiratory enzymes, and appreciated its fundamental importance in the oxidative processes of the cell. Then in 1937 Elvehjem and his associates isolated nicotinic acid and its amide from liver, and proved that it cured and prevented "black tongue" in dogs, a condition analogous to human pellagra. A few months later, three independent groups of investigators (5–7) established its efficacy in the treatment of pellagra, but it soon became evident that this disease was a symptom-complex associated with deficiency of several vitamins. It was learned that the frequent polyneuropathy was caused by lack of thiamin, while ariboflavinosis was responsible for angular stomatitis, bulbar conjunctivitis and facial seborrhoea. Niacin and its amide were found to relieve mental symptoms, mouth and mucous membrane lesions, and dermatitis (8, 9).

The term pellagra has since been reserved by some authorities for the symptoms and signs resulting from nicotinic acid (amide) deficiency (10–12), but with full realization that the latter: (i) may be precipitated by diets deficient in the protein component tryptophane (v.i.), (ii) is usually associated with a deficiency of one or more other vitamins, particularly thiamin and riboflavin (v.s.). The mechanism of pathogenesis of this vitamin deficiency state will now be considered.

2. Factors that May Produce Nicotinic Acid Amide Deficiency (Pellagra)

(a) *Precipitating Factors*

The factors that may precipitate nicotinic acid amide deficiency are similar to those that may precipitate deficiencies of other vitamins, and may be classified as follows (modified after Leitner (13) and others (10, 14)):

(i) *Inadequate Amount of Niacin Available in Diet* ("*Primary Deficiency*"). The average daily adult requirement of nicotinic acid is about 12 to 20 mgm. (15). The fact that the diet available contains less than this basic amount of niacin (and may or may not contain adequate amounts of other essential substances) may result from either (a) *inability to procure an adequate diet* (e.g. on account of famine, or for socio-economic reasons), or (b) *choice of a nutritionally unbalanced diet*, usually rich in carbohydrates and fats, but low in proteins, minerals and vitamins (e.g. due to ignorance, individual preference, or prescription by a physician).

(ii) *Interference with Ingestion* may be caused by a wide variety of conditions, both organic and "functional", which include the following: (a) any condition in which there is *anorexia or vomiting*, (b) *gastro-intestinal diseases*, (c) *psychiatric disorders* (e.g. psychoneuroses, both organic and functional psychoses, and addiction to alcohol or other drugs), (d) *neurological and traumatic disorders* that interfere with self-feeding, (e) *oral diseases* (e.g. sore mouth, or loss of teeth).

(iii) *Interference with Bio-synthesis*. Several of the constituents of the vitamin B complex, including nicotinamide, are known to be synthesized by the intestinal bacteria (16–20), and Ellinger *et al.*, have estimated that as much as 80 per cent. of the human requirement of niacin may be manufactured in the intestines. This normal synthesis may be impaired by several factors: (a) *inadequate intake of tryptophane*, which has been shown to counteract an induced need for nicotinic acid (21–24), and from which the latter is believed to be synthesized (20), (b) *ingestion of structurally similar compounds* (which may inhibit the formation of niacin by substrate competition). Thus such substances as maize, gelatin, phenylalanine and adenine have been shown to exert a pellagrogenic action (25–28), (c) *destruction of the bacteria responsible for bio-synthesis*, as by the "sterilizing" sulphonamides (e.g. sulphaguanidine and succinyl sulphathiazole) or by other antibiotics (such as penicillin or aureomycin).

(iv) *Interference with Absorption* may result from such conditions as the following: (a) *absence of the normal digestive secretions* (e.g. achlorhydria, which is frequently found in pellagra (29), obstructive jaundice, etc.), (b) *intestinal hypermotility*, as in various types of diarrhoea, (c) *reduction of effective absorbing surface*, due to disease, or surgical removal, of part of the gastro-intestinal tract, (d) *administration of drugs*, such as mineral oil, cathartics, or colloidal adsorbents.

(v) *Interference with Utilization* may be effected by: (a) *generalized interference with cellular metabolism*, which may be brought about by cellular toxins (e.g. "toxamins", alcohol, general anaesthetics, etc.), or by a variety of metabolic disorders such as hypothyroidism, diabetes mellitus, or any type of anoxia (anoxic, anaemic, stagnant, or histotoxic), (b) *specific inactivation of nicotinic acid*. In addition to their inhibition of biosynthesis, it is known that after absorption the sulphonamides exert an *anti-vitamin action* by substrate competition with *p*-amino-benzoic acid. There is some indication that there may be a similar competitive inhibition of nicotinic acid by closely related chemical substances (e.g. by some pellagrogenic agent that may be present in corn (23), or by isoniazid (30)).

(vi) *Interference with Storage*. While nicotinic acid compounds are widely distributed throughout the animal tissues, the concentration is highest in actively metabolizing tissues, particularly the liver. Hence any condition causing *impairment of liver function* may interfere with the amount of nicotinic acid retained in the body.

(vii) *Increased Excretion or Loss*: (a) *in the urine*. Nicotinic acid is normally excreted in the urine in the form of its methyl betaine (trigonelline), and in combination with glycine (nicotinuric acid) (110). The output by this route may be increased in such conditions as renal disease or diabetes (mellitus or insipidus). (b) *by other routes*. Substantial amounts of nicotinic acid and other vitamins may be lost during lactation, or with other body fluids (e.g. in serous exudates due to burns, or in severe loss of blood).

(viii) *Increased Nutritive Requirements* are present in a large number of conditions in which the metabolic rate is elevated above its usual level, amongst which are the following: (a) *hyperthyroidism*, (b) *periods of rapid growth*, (c) *pregnancy and lactation*, (d) *pyrexia*, from any cause, (e) any condition in which there is *increased muscular activity* (e.g. delirium), (f) several types of *treatment that may be prescribed by a physician* (e.g. high carbohydrate diets, or administration of glucose, insulin, thyroid, fever therapy, or stimulants such as caffeine or amphetamine).

(b) *Predisposing Factors*

The factors that predispose to the development of nicotinic acid amide deficiency (10, 31, 32) usually act by a combination of several of the mechanisms that have just been outlined, and will now be discussed briefly. These predisposing factors may be classified according to whether they are predominantly biological, psychological or social in nature. However, the observation that a given factor may be placed in two or even all three of these categories serves to emphasize that the integration of the individual is essentially bio-psycho-social.

(i) *Biological Factors.* A wide variety of somatic disorders that may cause the development of *pellagra secondary to organic disease* have already been mentioned in the preceding section, concerning the factors that may precipitate niacin deficiency. The somatic disorders that most commonly lead to the onset of this deficiency state are probably the following: (a) *gastro-intestinal diseases* are first in importance, and may produce pellagra by several mechanisms—usually by interference with ingestion, bio-synthesis and/or absorption. Mann and Stare (33) state that "probably the most frequent contributing cause in nutritional deficiency is diarrhoea". In this connection, it is also interesting to note Hardwick's clinical deduction (34) that upper intestinal disorders are prone to result in thiamin deficiency, whereas lower intestinal disorders are more likely to lead to nicotinic acid deficiency, (b) *diseases causing increased nutritive requirements*, often only temporary in nature (particularly acute infections, and delirious states), (c) *surgical operations* are almost invariably accompanied by at least temporary interference with both ingestion and utilization (in cases receiving general anaesthesia), and may also be complicated by a number of other factors that may precipitate niacin deficiency.

(ii) *Psychological Factors.* Psychiatric disorders, both organic and functional in nature, frequently lead to the onset of a secondary vitamin deficiency due to ingestion of a nutritionally unbalanced diet, or to an overall interference with ingestion (e.g. on account of anorexia, or delusional ideation). However, psychological factors are also causally related both to somatic pathology ("psychosomatic disease") (35), and to social factors (such as the poverty and ignorance cited below) (36), and hence may indirectly contribute to the development of nutritional deficiencies by a wide variety of mechanisms.

(iii) *Social Factors. Famine, poverty and ignorance* are the factors held responsible for the development of endemic pellagra. In these cases, the main mechanism of production of the deficiency is the presence of an inadequate amount of the vitamin, or its precursor tryptophane, in the diet ("primary deficiency"—v.s.)—either through inability to procure an adequate diet, or choice of a nutritionally unbalanced diet, or both—but the lack of niacin may also result from interference with bio-synthesis by ingestion of pellagrogenic substances such as maize.

(iv) *Alcoholism.* The existence of a close association between alcoholism and pellagra was emphasized by Klauder and Winkelmann (37) in 1928. A few years later, in an analysis of 102 cases of pellagra, Boggs and Padget (38) found that about 30 per cent. were of the senile type (v.i.), 39 per cent. were postalcoholic, and in about 30 per cent. the disease had arisen as a complication of some other malady (v.s.). In patients developing *alcoholic pellagra* ("pseudo-pellagra"), there has almost invariably been prolonged inadequate nutrient intake (due to both ingestion of a nutritionally unbalanced diet, and to an overall reduction in intake), and probably also interference with bio-synthesis, absorption and/or storage (due to gastro-intestinal and hepatic dysfunction). However, in addition, a clinical deficiency state may be precipitated by other mechanisms (e.g. an increase in nutritional requirements, when the alcoholism has been complicated by delirium tremens or organic disease—v.s.).

(v) *Senility*. Boggs and Padget (38), Gottlieb (69) and others have drawn attention to the frequent occurrence of pellagra, or aniacinosis, in senility. Mild degrees of vitamin deficiency are probably usual in elderly persons, for which there appear to be a number of reasons. Inadequate nutrient intake is common, and may be attributed to socio-economic factors, psychological dysfunction (on an organic or functional basis) and/or somatic disease. In addition, there may be interference with absorption, utilization and/or storage, and a clinical deficiency state is often finally precipitated by some minor acute organic disease (v.s.).

3. THE NEURO-PATHOLOGY AND PSYCHIATRIC MANIFESTATIONS OF PELLAGRA

Following a recent clinical and neuro-pathological study of 14 fatal cases of pellagra, and a review of the relevant literature, Leigh (39) concluded that the term "pellagra" was no more than a generic title, embracing several nutritional deficiency syndromes of differing aetiology. In the syndromes consisting of weight-loss, diarrhoea, dermatitis of exposed surfaces, and mental changes, a retrograde cell degeneration of the Betz cells was the only constant pathological finding. The cells of the pontine, dorsal vagal, gracile and cuneate nuclei also showed a similar change, but were less constantly affected than the Betz cells. Clinically, he observed that loss of weight (which was sometimes very marked) commonly preceded the onset of both diarrhoea and dermatitis. It has also been found that the mental signs of mild niacin deficiency, or *pellagra sine pellagra*, often occur in the absence of any dermatologic, mucous membrane, or gastro-intestinal symptoms (12, 13, 65–67, 81).

The mental signs of pellagra may be regarded as those of either an acute ("toxic") or chronic organic reaction (40, 41)—*primary signs of organic brain dysfunction* (varying degrees of impairment of intelligence, memory and consciousness; with disinhibition, emotional lability, disorientation, confusion, perseveration, confabulation, delirium or stupor, and a decreased tolerance to toxic substances)—and *secondary functional signs* due to exaggeration of previous personality characteristics (often depressive or paranoid tendencies), or to the release of overt symptomatology of a hitherto latent functional psychosis or psychoneurosis. Both the physical lesions of pellagra and the signs of organic brain dysfunction are frequently preceded by psychoneurotic symptoms of this type. McLester, Sydenstricker, Spies and others (8, 10, 13, 15, 42–46, 81) have described syndromes of neurasthenia and hypochondriasis, similar to those caused by thiamin deficiency (47–54), and characterized by such symptoms as fatigue, anorexia, insomnia, headaches, vertigo, palpitation, anxiety, apprehension and depression.

Of all the possible mental changes in pellagra, those most commonly recognized consist of three syndromes (10, 20, 55, 56), which may justifiably be designated "the three D's": *Depression* (with or without signs of organic brain dysfunction), *Delirium* (an acute, reversible, "toxic" reaction) and *Dementia* (a chronic, irreversible, organic reaction). However, the diverse and protean nature of mental disorders associated with pellagra has long been appreciated, and Singer (57) in 1915 separated them into the following groups: (*a*) disorders directly due to the pellagrous syndrome (symptomatic depressions, and delirious states), (*b*) disorders based on peculiarities in personal make-up, precipitated by pellagra (manic depressive psychoses, dementia praecox, and the psychoneuroses), (*c*) disorders due to definite brain changes, with pellagra as a complication (arteriosclerotic dementia, senile and presenile psychoses, and general paresis). Subsequent observations have indicated that pellagra and other nutritional deficiencies (i) may not only precipitate functional disorders, but also result from them (when they cause inadequate nutrient intake—v.s.), (ii) may be at least partly responsible for the development of certain of the organic psychoses enumerated above, as well as occurring as a complication of them (66, 70).

Pellagra in infancy and childhood. Pellagra is not uncommon in infancy and childhood (10, 15, 58–61), but the mental signs and symptoms differ slightly from those found in adults. Affected children lack the spontaneous laughter and tireless energy of normal children. They are listless, apathetic and tired, but are also usually irritable, easily frightened, apprehensive, fretful, and apt to cry frequently. In cases of any duration, there is both *physical and mental retardation* (with impairment of intelligence, memory and concentration), and in older children there is consequently a rapid decline in progress at school. In very severe cases confusion, hallucinations and delirium occur, as in adults, and may be followed by coma and death. Appropriate treatment causes the disappearance of the delirium, but in some cases the child thereafter remains permanently retarded (61). Carothers (62) has pointed out that "malnutrition in prenatal life and infancy may interfere with neurone development, and, in early childhood, may incapacitate the children at the very time when they should be most adventurous and curious; in either case, it is likely to result in a backwardness which cannot be readjusted later".

SECTION B: NICOTINIC ACID THERAPY IN PSYCHIATRIC DISORDERS—A CLINICAL REVIEW

1. NICOTINIC ACID THERAPY IN THE PSYCHIATRIC MANIFESTATIONS OF PELLAGRA

Since its first application to the treatment of human pellagra, considerable evidence has accumulated, confirming the initial reports that nicotinic acid effected prompt improvement both in psychotic and in psychoneurotic syndromes occurring in this deficiency state (8, 42–45, 63–65). Hardwick (66) and others have also drawn attention to the frequency of pellagra and related deficiency states in psychiatric practice.

In a review of vitamin B deficiency and nervous disease published in 1939, Aring and Spies (65) discussed the results of niacin therapy in over 300 such pellagrins having various psychiatric manifestations. In 70 patients with acute organic psychoses, that had been present from 1 to 83 days, nicotinic acid effected complete recovery. In 13 patients with chronic organic psychoses, uniform improvement was noted. No chronic pellagrous psychoses of many years duration wholly resolved, but something approaching a cure was achieved in two cases hospitalized for about nine months. In 225 mild pellagrins, symptoms typical of neurasthenia were completely relieved. These authors emphasized their observations that many persons develop mental signs of pellagra, at least to a mild degree, long before they show any other signs of the disease.

2. NICOTINIC ACID THERAPY IN "TOXIC" PSYCHOSES ATTRIBUTED TO NUTRITIONAL DEFICIENCY

In the same article (65), Aring and Spies recorded that niacin had effected prompt relief in 71 further cases, with mental changes ranging from psychoses to stupor, but with no clinical evidence of pellagra other than malnutrition (and in most cases a positive test for porphyrins or related substances in the urine). At about the same time, Cleckley, Sydenstricker and Geeslin (67) obtained beneficial results from the use of nicotinic acid in the treatment of 19 patients with comatose and stuporous states. These patients lacked the typical physical signs of pellagra, but showed evidence of toxicity or dehydration, and were regarded as having atypical psychotic states associated with malnutrition.

Two years later, however, Sydenstricker and Cleckley (68) reported a series of 29 cases, all having severe psychiatric symptoms of a confusional nature, and none having any of the physical signs of either pellagra or malnutrition. Only one had a previous history of pellagra, and in this case there had been no evidence of the disease for several years. Half of the cases in this series were lethargic or stuporous, but about a third were actively disturbed. It is interesting to note that about two-thirds were in the presenile or senile age range. The majority of these patients underwent prompt and often very impressive improvement after treatment with nicotinic acid, and the authors felt that, while these cases might ordinarily have been diagnosed as toxic psychosis or exhaustion delirium, the real cause was probably an avitaminosis sufficiently severe to produce a psychosis, but without any other indication of its presence. Seven patients underwent some degree of improvement only, one remaining psychoneurotic, while the other six showed persistent intellectual and emotional impairment, which was apparently related to cerebral arteriosclerosis, senility, or other factors. Even in these patients, it was felt that a deficiency of nicotinic acid was in part responsible for the psychiatric condition, and it was concluded that a therapeutic trial with nicotinic acid was indicated in toxic psychoses, exhaustion delirium, and other confusional psychoses of doubtful aetiology.

Gottlieb (69) in 1944 described five cases of mental confusion or stupor, occurring in middle-aged or elderly persons. These cases responded to niacin therapy, and he considered their condition to be one of "aniacinosis", emphasizing the following aetiological factors: senility (associated with inadequate nutrient intake, and following acute illness or surgical operations), chronic alcoholism (with anorexia, gastritis, and interference with absorption), and gastro-intestinal disturbances (both organic and functional). The following year, Musselman (70) reported that delirium, occurring in cases of deficiency disease when complicated by acute infections such as malaria or dysentery, was relieved by nicotinic acid and thiamin.

More recently, Foster (71) reviewed the results of therapy in 40 patients with "toxic psychosis" (an organic reaction, with memory defect and disorientation, etc.), who received nicotinamide and measures designed to correct hepatic insufficiency. Twenty of these patients were admitted to hospital because of the toxic psychosis, 11 were surgical patients who developed a toxic psychosis post-operatively, and the remaining 9 patients had functional depressions on which symptoms of a toxic psychosis were superimposed. It is noted that 23 of these 40 patients were over the age of 60. As a result of his investigation, the author reached (amongst others), the following conclusions: Toxic psychosis on a nutritional basis may occur without any physical signs of vitamin deficiency. If nicotinamide therapy is commenced immediately after the onset of the psychosis, and adequate diet restored, the response may be very rapid and dramatic. In cases of longer duration, response to nicotinamide may be slow and may not occur until normal liver metabolism is restored, which may take some months. When the latter was restored, several patients recovered without massive doses of nicotinamide. All long-standing cases showed liver insufficiency, and the mental state did not return to normal until there had been improvement in liver function. In depressed patients with nutritional deficiency, E.C.T. was of no value until the deficiency had been corrected. The author also proposed the term "nutritional psychosis" for toxic psychosis accompanying deficiency diseases.

3. Nicotinic Acid Therapy in Encephalopathies Commonly Associated with Alcoholism

Attention has already been drawn to the existence of a close association between alcoholism and pellagra (37), and the fact that 39 per cent. of the cases of pellagra recorded by Boggs and Padget (38) were postalcoholic. Biochemically, Dewan (72) has shown that nicotinic acid and riboflavin are essential for brain to metabolize alcohol, and niacin therapy has been felt to be of value in some cases of delirium tremens (68). The role of niacin will now be discussed in two syndromes which are closely related to each other—nicotinic acid deficiency encephalopathy, and Wernicke's encephalopathy. Both these syndromes: (i) have been frequently (though by no means invariably) associated with alcoholism, (ii) have been reported to respond favourably to niacin therapy (either with or without other therapeutic agents (73–77)), (iii) have been attributed, either wholly or partially, to deficiency of niacin (73–74). These encephalopathic states have been considered by some authorities to be identical (73–74), but Jolliffe and his associates (76–77), Spillane (81), and Hardwick (82) have regarded them as distinct entities.

(a) *Nicotinic Acid Deficiency Encephalopathy*

Jolliffe, Bowman, Rosenblum and Fein in 1940 reported 150 cases of a syndrome, which they termed "nicotinic acid deficiency encephalopathy" (75–76), and which was characterized by clouding of consciousness, cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes. Bender and Schilder (79), who had previously described its clinical picture, had included this syndrome as one of a group of five which they had called collectively "encephalopathia alcoholica". However, while most of their subjects were alcoholics, Jolliffe and his associates pointed out that their encephalopathic syndrome did not occur exclusively in alcoholic patients. It was observed in association with pellagra, polyneuropathy, scurvy, ariboflavinosis, delirium tremens or the Wernicke syndrome (76–77). Only half of their series of 150 cases showed other signs of nicotinic acid deficiency. When these patients were treated with routine diet and parenteral fluids, with or without additional thiamin therapy, 95 per cent. died. Mortality (from the condition itself) was reduced to 50 per cent. by feeding a vitamin rich diet, and giving concentrates of whole vitamin B complex, in addition to parenteral fluids. A further substantial reduction in mortality—to 15 per cent.—was brought about when patients were given only a basal diet and parenteral fluids, but these measures were supplemented by niacin therapy.

Sydenstricker (73) subsequently commented on having seen a number of instances of this encephalopathy, and confirmed the striking effects of nicotinic acid in promoting rapid improvement. However, in spite of the dramatic reduction in mortality thus achieved, the recovery of mental function was found to be incomplete in a large proportion of these cases. Bowman and Wortis (80) drew attention to the fact that many patients who remained alive after receiving niacin therapy retained signs of permanent organic brain dysfunction. From these and similar observations, it has been concluded that reversible changes in cellular function of the brain ("*biochemical lesion*") may readily progress to irreversible structural changes ("*morphological lesion*") (10, 64, 67, 80–83, 98). Hence, "it does not necessarily follow that the failure of vitamin therapy to reverse a pathological process means that the disease is unrelated to deficiency of the vitamins" (82).

In his book on nutritional disorders of the nervous system, Spillane (81) remarks on the similarity between some of the case reports on acute encephalopathic states attributed to nicotinic acid deficiency and some of the older accounts of "typhoid pellagra". He goes on to speak of the dramatic response to nicotinic acid that he had observed in indigent Arabs in the Middle East, admitted to hospital unconscious, and having a variety of signs of neurological involvement including tetanic spasms of the body, tremors and rigidities of the limbs, grasping and groping movements, and writhing of the lips and tongue, sometimes with loud sucking sounds. While the immediate results of nutritional therapy in these cases was good, he considered the ultimate prognosis poor.

Spillane also mentions having seen stupor, delirium and acute psychotic symptoms in some of the German patients taken prisoner in the Channel Isles in 1945. These cases responded well to treatment, but since they received whole vitamin B complex, it was not possible to deduce a deficiency of niacin. Moreover, the majority apparently did not demonstrate the specific syndrome of neurological manifestations referred to by Jolliffe *et al.* as nicotinic acid deficiency encephalopathy.

(b) *Wernicke's Encephalopathy*

Wernicke (84) in 1881 described a syndrome characterized by clouding of consciousness, varying ophthalmoplegias, and ataxia, which was associated with acute superior haemorrhagic polio-encephalitis. In 1938, Alexander, Myerson and Pijoan (85) produced Wernicke's pseudo-encephalitis in the pigeon by feeding diets low in vitamin B_1 and high in other vitamins, and Alexander (86) subsequently showed the identity of these experimental lesions with the lesions of haemorrhagic polio-encephalitis occurring in chronic alcoholism in man.

Campbell and Biggart (87) pointed out that a significant number of these cases occurred as a complication of conditions other than alcoholism, and Jolliffe, Wortis and their associates studied 34 cases of the Wernicke syndrome, three of which were in non-alcoholics (77–78). The latter group found polyneuropathy, considered due to thiamin deficiency, to be present in all instances, and nicotinic acid deficiency encephalopathy in approximately a third of their cases. Whenever appropriate specific therapy (e.g. thiamin, or nicotinic acid) was given early enough, improvement or cure resulted. From their own observations, and a review of the literature, these authors reached (among others) the following conclusions: The syndrome originally described by Wernicke is probably a combination of several nutritional deficiencies affecting the nervous system. It is invariably associated with a deficiency of thiamin (78), but there is usually a lack of other nutritive essentials (one of these being niacin). The ophthalmoplegia is due to a thiamin deficiency, and is always preceded or accompanied by peripheral neuropathy. The clouding of consciousness may be related to anything which interferes with proper cerebral metabolism (e.g. lack of carbohydrate, oxygen, thiamin, niacin or riboflavin). Delirium frequently precedes the onset of this syndrome, and in recovered patients the development of a Korsakoff syndrome is the rule.

A number of other contributions have since been made towards the further understanding of Wernicke's encephalopathy, but most of them fall outside the scope of the present article, whose concern with the latter syndrome is confined to the role of nicotinic acid in its causation or treatment. However, it may be relevant to mention here that Meyer (88) has drawn attention to an apparent negative correlation between the neuropathology of this syndrome and of pellagra. Currently accepted formulations on the aetiology of Wernicke's encephalopathy (74, 81–82) tend to concur substantially with that of Jolliffe, Wortis *et al.* (vide supra) in emphasizing the presence of thiamin deficiency, but in recognizing the likelihood of associated deficiencies (particularly of niacin or other members of the vitamin B complex).

4. Nicotinic Acid Therapy in Organic Psychoses Associated with Senescence and Senility

Reference has already been made to the fact that mild degrees of vitamin deficiency are probably usual in elderly persons, and to the observation of Boggs and Padget (38) that nearly a third of their cases of pellagra were of the senile type. In the past fifteen years numerous accounts have appeared of improvement in mental confusion and other signs of organic psychoses occurring in senility, following the administration of nicotinic acid and other metabolic agents.

Wexberg (89–90) in 1941 analysed in some detail the manifestations of neurometabolic deficiency in old age (for which he proposed the term "senile encephalomyelosis"). Evidence of brain involvement consisted of mental confusion, ranging from mere disorientation as to time to delirium with clouded sensorium, extreme restlessness, hallucinations, severe anxiety, and frequent paranoid delusions. The onset was acute or subacute, and often superimposed upon an already existing senile or arteriosclerotic dementia. It was found that improvement of the mental disorder or complete recovery under treatment with thiamin chloride, nicotinic acid, and liver extract, was sometimes very dramatic —being observed occasionally even in apparently moribund patients—and occurred in some cases of senile delirium in which no physical signs of deficiency were present.

Similar results were achieved the same year in a controlled experiment by Stephenson, Penton and Korenchevsky (91), who administered vitamins B and C to 40 patients suffering from senile dementia. Improvement in the mental condition was recorded in 25 of these patients, in that they were less incoherent and more intelligent in their talk, less depressed or less excited, brighter, more friendly and sociable, less quarrelsome, cleaner in their habits, recognized relatives and nurses, performed better work, and showed improvement in nocturnal insomnia and day sleeping.

Other authors have observed striking improvement in organic psychoses occurring in senescence or senility following the administration of nicotinic acid alone. Thus it has been noted earlier that about two-thirds of the cases in the series reported by Sydenstricker and Cleckley in 1941 (68) were in the pre-senile or senile age range, and Gottlieb's cases of "aniacinosis" (69) also belonged to the same age group. Meyersburg (92), Shock (93), Sebrell (94) and others have pointed out that many of the psychiatric manifestations of the organic psychoses of senility are similar to those of nutritional deficiency, particularly pellagra ("pellagrous encephalopathy"), and that fatal results usually follow failure to institute appropriate therapy in the latter condition.

There has been considerable difference of opinion as to whether niacin therapy effects improvement in the psychoses attributed to cerebral arteriosclerosis and senile atrophy. Many physicians have felt that niacin is of value in such cases only when there is an associated or relative deficiency of this vitamin but this view has not been definitely established. Amongst authors who have recommended a therapeutic trial with niacin in cases with one or other of these diagnoses may be mentioned Sydenstricker and Cleckley (68), Caldwell and Hardwick (95), Strecker, Ebaugh and Ewalt (96) and Lehmann (83). Three comparatively recent articles of relevance to this question are discussed below.

Moore, Morris, Smith and Lawson (97) in 1951 announced the development of a programme for the treatment of psychosis with cerebral arteriosclerosis, with special emphasis on the intravenous administration of histamine and nicotinic acid. These drugs were each administered on alternate days with the intention of effecting cerebral vasodilatation, and their preliminary report indicated very promising clinical results. Out of 24 patients with symptoms of organic brain disease, who were considered to have received adequate treatment, all but one improved. After the termination of intravenous therapy, an attempt was made to maintain this improvement by the use of oral nicotinic acid. The patients were subjected to re-evaluation of their condition at least ten months after the discontinuation of intravenous medication, and at this time it was found that 1 patient remained in hospital unchanged (he also had C.N.S. syphilis), 2 patients had improved but remained in hospital (now requiring general medical rather than psychiatric care), 5 patients had undergone improvement initially, and were at home but had remained essentially unchanged since leaving hospital, 3 patients were at home and had continued to improve after their return, 8 patients were at home showing marked clinical improvement or working part time, and 5 patients were at home, markedly improved, working full time. The authors also pointed out that, as the confusion and disorientation improved, a number of their cases became increasingly depressed, and E.C.T. was administered to a total of 9 out of the 24 cases evaluated above. In some of the latter cases there was a return of confusion, but further histamine-nicotinic acid therapy seemed to produce a rapid remission of the post E.C.T. confusion.

Gregory (98) administered large doses of nicotinic acid (300 mgm. 3 times a day by mouth, and 100 mgm. parenterally daily) to a series of patients of both sexes having organic psychoses of senility (senile psychosis, and psychosis with cerebral arteriosclerosis), immediately following their admission to a private mental hospital (when they were also receiving a highly nutritious diet containing liberal supplies of other vitamins). An attempt was made to evaluate the *degree of improvement* that might be anticipated in these cases, and the *proportion of patients* in which a given degree of improvement might be expected to occur. Systematic psychiatric examinations (with particular reference to orientation, memory, and secondary functional symptoms), supplemented whenever possible by psychological tests of intellectual function, were performed before the commencement of niacin therapy, and were repeated after maximal improvement (if any) had occurred. Every effort was made (by means of detailed enquiry from relatives, as well as relevant somatic investigations) to establish the diagnosis beyond reasonable doubt, and particularly to exclude possible toxic aetiological factors. However, it was recognized that this is difficult in elderly subjects with confusional psychoses, since protracted cerebral decompensation may be precipitated by quite transient and minor disorders of metabolism (such as relatively mild infections, intoxications, anoxic episodes, or nutritional deficiencies).

Analysis of the results of therapy in these patients tended to corroborate certain empirical impressions derived from previous experience with much larger numbers of similar cases. The *proportion of patients* with psychoses of senility that underwent marked improvement during treatment bore a close relationship to their age. Out of 14 patients up to and including the age of 65, 8 showed either dramatic or significant improvement. Out of 40 patients over the age of 65, however, only 4 improved to a comparable degree. The *degree of improvement* observed was infinitely variable, being limited by residual signs of permanent organic brain dysfunction, similar to that described by Bowman, Wortis and others (10, 65, 68, 80–83)—vide supra. It was concluded that the final level of intellectual function attained in these cases was related to two independently varying factors—namely, the initial intelligence, and the severity of the residual organic mental dysfunction (resulting from irreversible structural changes, or "morphological lesion"). After consideration of a number of possible factors involved in the causation of the latter, Gregory proposed certain *tentative criteria for the estimation of prognosis* in these cases (98). He postulated that the degree of improvement (or final level of intellectual function) in any individual case could frequently be predicted by assessment of the following (and possibly other) factors:

(i) former *intelligence* (the prognosis being better in those whose former intelligence was high),

(ii) *age* (the prognosis being better in younger patients),

(iii) *duration of psychosis* at commencement of therapy (the prognosis being better in cases of recent, and fairly rapid, onset),

(iv) a clinical *diagnosis* of "psychosis with cerebral arteriosclerosis" (carrying a more favourable prognosis than that of "senile psychosis"),

(v) a psychosis with pronounced *secondary* (*functional*) *signs*, particularly of depression (carrying a more favourable prognosis than a psychosis with only primary signs of organic confusion),

(vi) adequate dosage of niacin, and *administration* for a sufficient length of time.

It is interesting to apply these prognostic criteria in retrospect to the series of cases recorded by Moore *et al.* (97), which has been reviewed earlier. While the high proportion of cases in this series that underwent improvement may be attributed to differences in therapeutic technique (and possibly also diagnostic criteria) several of the above factors are applicable, and may have indicated a relatively favourable prognosis *ab initio*: (*a*) age—only two of these patients being over the age of 65, (*b*) diagnosis—all having a clinical diagnosis of "psychosis with cerebral arteriosclerosis", (*c*) secondary signs of depression. In one-third of these patients (8 out of 24) the psychosis was considered "predominantly affective", and 6 of this group (75 per cent.) were markedly improved following treatment. The remaining two-thirds of the patients (16 out of 24) were considered "predominantly cognitive", and only 7 of the latter group (approximately 45 per cent.) underwent marked improvement.

One further article concerning niacin therapy in the organic psychoses of senility is mentioned here, in view of its recency and some apparent variance with the two that have just been discussed. Levy (99) has published an account of the administration of various combinations of three drugs to 30 aged mental hospital patients, 21 having primary diagnoses of chronic brain syndrome with cerebral arteriosclerosis or senility, and the remainder being felt to have senile changes overshadowing their original mental disturbances. All were over the age of 60, and the average duration of hospitalization was 7 years, the shortest stay in hospital being 9 months. The three therapeutic agents consisted of cytochrome C, leptazol (metrazol) and nicotinic acid, and were chosen for their stimulatory, vasodilatory and enzymatic properties. Levy found that nicotinic acid alone, which he employed in doses of 100 mgm. orally 3 times a day with the intention of producing vasodilatation (although it must be noted that this dosage effects relatively little vasodilatation), was ineffective therapeutically, as were each of the other two drugs when administered singly. However, when the same doses of nicotinic acid and leptazol as had been given separately were prescribed in combination, he observed both objective and subjective improvement in these patients, with a marked improvement in behaviour and a definite (though less remarkable) increase in intellectual function (the average gain in the Wechsler-Bellevue intelligence quotient being 6 points). In this connection, the relatively minor improvement in the intellectual function of a large proportion of the patients in this series might have been predicted, in view of the diagnoses and duration of confusional symptomatology (and possibly also the dosage of drugs employed).

It remains to be pointed out that considerable further controlled research is indicated into the efficacy of various therapeutic agents in this important group of organic psychoses of senescence and senility—which constituted over 15 per cent. of the first admissions to Canadian mental institutions (exceeded only by schizophrenia) in a typical recent year (100). It would also be of interest to learn the relationship (in the causation and treatment of these disorders) of niacin to other enzymatic or vasodilator drugs, including niacinamide (which possesses the same vitamin properties, but does not produce vasodilatation—vide infra).

5. Nicotinic Acid Therapy in Psychiatric Disorders Apparently Unrelated to Nutritional Deficiency

Nicotinic acid deficiency of varying degree or duration has been held to be either wholly or partially responsible for the development of all psychiatric manifestations that have been ameliorated by administration of this substance —including all the disorders hitherto discussed. However Wexberg (90), Lehmann (83), and others have concluded that it is not justifiable to postulate such a deficiency merely on the basis of a successful therapeutic test with nicotinic acid, since the latter may exert a beneficial effect by means of other mechanisms or modes of action (vide infra).

Apart from some of the cases already reviewed, there have been several reports of favourable results from niacin therapy in cases of both organic and apparently functional disorders in which no evidence of nutritional deficiency was discovered. Thus Lehmann (101), in 1944, described a case of post-traumatic confusional psychosis that resolved completely following administration of massive doses of niacin. The patient was a forty-three year old man who had suffered concussion in an accident, had remained in a state of confusion for the following nine weeks, and had undergone gradual mental deterioration in spite of several types of treatment. Careful enquiry into his previous history, together with thorough physical examination and laboratory investigation, failed to reveal any nutritional deficiency or other aetiological factor apart from cerebral trauma. In addition to establishing the diagnosis beyond reasonable doubt, special care was taken to ascertain whether the patient's improvement was really due to the administration of niacin, and was neither spontaneous and coincidental, nor resultant from other physical or psychological factors. He was examined several times daily, both psychiatrically and by means of psychological tests, throughout the course of treatment as well as for some time previously. The changes in his condition were dramatic and almost immediate. A definite improvement in memory was noted on the second day of niacin therapy, and all major symptoms of organic mental impairment resolved within a week. The patient had wholly recovered by the end of a month, and was able to leave hospital and resume his former employment as an accountant.

The same author has drawn attention to the use of nicotinic acid in combination with other drugs—and, to a lesser extent, alone—for sedating patients with organic brain disease and senile disturbances (102). By administering a preparation containing nicotinic acid and minimal doses of several sedative drugs, having different sites of elimination or detoxification and varying duration of action, it was found possible to avoid the marked and sometimes prolonged increase in mental confusion that commonly follows the administration of an effective dose or a single sedative to a patient of this type. At the same time, the overall sedative effect of the combination of drugs was rendered adequate through synergistic action of its components.

A further therapeutic application of niacin mentioned by Lehmann (83) is its administration to patients exhibiting more than the usual amnesia following electro-convulsive therapy. Its use in this syndrome has been corroborated by Furtado, and Moore *et al.* (97), amongst others, and niacin has also been considered of some value in cases of prolonged insulin coma (103) and in the confusional state that may follow the latter.

In many of the psychiatric disorders found by earlier workers to respond to niacin therapy, depression is frequently a prominent feature (e.g. organic psychoses occurring in classical pellagra, psychoneurotic syndromes due to mild niacin deficiency, organic psychoses of senescence and senility, and other toxic or organic reactions), but this substance has also been applied to the treatment of apparently functional depressions. In an article published in 1950, Washburne (104) described the use of nicotinic acid as a pharmacological adjunct to psychotherapy in patients with various types of depression, almost all functional in origin. Out of 29 patients receiving this treatment, the results in 14 (which included those believed to have a high degree of suggestibility) were considered inconclusive. The remaining 15 patients were all university students between the ages of 18 and 46. In this group, all but one showed a marked elevation in mood and activity-level within a few days of commencing niacin therapy, and none of them relapsed while taking the drug. Eleven of them required further treatment at a later date, but in each instance an improvement identical with the first occurred on repeating the medication. The author felt that no conclusion could be drawn from the improvement observed in this small group of patients, but that the results were of sufficient uniformity to render further investigation desirable.

Another article has since appeared, in which Thompson and Proctor (105) recorded their experience in the use of nicotinic acid together with phenobarbital in the management of depressive and anxiety reactions. Initially they used nicotinic acid alone, but were not impressed with the response of depressive patients, and observed that those presenting a mixture of depressive and anxiety symptoms responded better. They then administered a combination of nicotinic acid with phenobarbital and selected for study the first 100 patients so treated, who ranged in age from 21 to 60. Tablets containing nicotinic acid 100 mgm. and phenobarbital 8 mgm. were given in doses of ½ or 1 tablet at 3 successive intervals before meals for 21 days. The results were based as objectively as possible on clinical observation and what the patients and their families reported, reliable follow-up histories being available in 91 of these cases. 34 per cent. of the cases studied showed "definite improvement" during treatment, being relieved of most of their symptoms, and requiring no further intensive treatment. A further 47 per cent. were considered to have undergone "some improvement" but required other treatment.

It would appear that further research is indicated into the administration of nicotinic acid to patients with functional psychiatric disorders, as well as the organic disorders discussed previously, but that such research would be rendered more valuable by comparison of the results with those obtained in similar series of untreated controls.

SECTION C: THE ACTIONS AND ADMINISTRATION OF NICOTINIC ACID

1. Pharmacology: Postulated Actions of Nicotinic Acid

Several possible modes of action will now be considered, by which niacin may effect improvement in various psychiatric disorders: (*a*) elimination of an existing vitamin deficiency, (*b*) mass action on cellular metabolism ("saturation effect"), (*c*) cerebral vasodilatation with increased blood supply to the brain, (*d*) other actions—physical and psychological.

(a) *Elimination of an Existing Vitamin Deficiency*

The normal metabolism of the nervous system (106) is dependent, among other things, on: (i) an adequate supply of oxygen, (ii) an adequate carbohydrate substrate, (iii) intact enzyme and coenzyme systems. Glucose is the main substrate utilized in the respiration of the grey matter, and studies have shown that 80 to 90 per cent. of the normal respiration of the brain can be accounted for by glucose consumption (107). The vitamins thiamin, riboflavin and nicotinic acid are essential constituents of certain of the tissue enzymes involved. Nicotinic acid is pyridine carboxylic acid, and its amide is present as a prosthetic group in the di- and tri-phosphopyridine nucleotides (DPN and TPN) known as coenzymes I and II (cozymase (108) and coferment (109)) respectively (110, 111). It has been established that these two coenzymes are involved in both glycolysis and respiration (112).

Now, although nerve fibres can contract a small oxygen debt, grey matter cannot do so, and is highly susceptible to deprivation of its supply of oxygen, glucose or essential vitamins (106). If there is a deficiency of one or more of these essential substances, reversible changes in cellular function occur ("biochemical lesion"), which may progress to irreversible structural changes ("morphological lesion"). Such disorders of function or structure of the brain are accompanied by evidence of disordered psychological functions (e.g. perception, ideation and behaviour). The impairment of various psychological functions due to anoxia has been studied extensively (113), and it is known that similar manifestations result from hypoglycaemia, or from deficiency of one of the constituents of the enzyme or coenzyme systems, including nicotinic acid.

At least one action of nicotinic acid in any psychiatric disorder in which it is administered must be the elimination of any existing deficiency of this vitamin, and the restitution of disordered cellular metabolism. Some investigators have concluded that this is its only mode of action, and that there must be some relative or associated deficiency of nicotinic acid in every syndrome in which it is genuinely beneficial. However, several other possible mechanisms of action have been postulated, and are discussed below.

(b) *Mass Action on Cellular Metabolism* (*"Saturation Effect"*)

It has been suggested that massive doses of niacin may produce their beneficial action, in syndromes where there is no deficiency of the vitamin, through some kind of "saturation effect" (83). In the latter instance, it would still be operating through a direct action on cellular metabolism, though not by replacement of a deficient factor. Certain evidence in support of this possible mode of action will now be considered.

It has already been noted that coenzymes I and II are involved in both glycolysis and respiration (112), and this is perhaps illustrative of the intimate functional interrelationships of the various substances essential for the metabolism of brain. Thus deficiency of one such essential substance may cause deficiency of another—hypoglycaemia, for example, has been shown to cause profound anoxia (114). Moreover, the impairment of function caused by deficiency of one such essential substance may be partially corrected by the administration of another such substance without the initial deficiency being corrected. Thus McFarland and others (113) found that the impairment of visual sensitivity caused by hypoglycaemia was counteracted by administration of oxygen, and conversely that administration of glucose tended to reduce the impairment in visual sensitivity brought about by anoxia.

It would be reasonable to suppose that a similar effect might occur following administration of nicotinic acid, and the results of several experiments tend to confirm this supposition. Morell (115) in 1940 noted that nicotinamide produced an increase in the capacity for hard muscular exercise at sea level, and Frankau (116) in 1943 observed acceleration of co-ordinated muscular effort by the same substance.

Calder (117) in 1948 suggested on theoretical grounds that the enzymatic phases of cellular respiration might constitute a protective mechanism, useful in tiding the animal organism over a temporary period of reduced oxygen tension, and that this might well be the device by which the tissues were enabled to accumulate an "oxygen debt" during excessive muscular exercise. The effectiveness of this mechanism would depend on an adequate supply of oxidized coenzyme, and if part of the latter were trapped in the reduced state because of lack of oxygen, the administration of nicotinic acid might augment the available supply of coenzyme, and thus partly correct the induced deficiency. He therefore investigated the effects of nicotinic acid on anoxia in rats subjected to low barometric pressures. He found that rats treated with nicotinic acid or its amide were able to survive a greater degree of anoxic anoxia than untreated controls. Similarly, the tachypnoea developing at low barometric pressure (with diminished oxygen tension) was much less in treated than in untreated rats.

(c) *Cerebral Vasodilatation, with Increased Blood Supply to the Brain*

In addition to the two preceding actions on cellular metabolism—the former established and the latter hypothetical—niacin has a pronounced systemic action. Smith, Ruffin and Smith (6), together with other pioneers in its application to the treatment of pellagra, observed marked vasodilatation following the administration of niacin, but not niacinamide. Abramson, Katzenstein and Senior (118), using the venous occlusion plethysmograph, demonstrated that increased bloodflow occurred through the arm, and to a lesser extent through the leg, following oral or intravenous administration of nicotinic acid. There has since been considerable controversy as to whether this vasodilatation affects the cerebral vessels, and, in the latter event, whether the increased blood supply associated with such cerebral vasodilatation is responsible for the beneficial effects of niacin therapy in some psychiatric syndromes.

Moore (119) in 1940 reported that nicotinic acid caused an increase in cerebrospinal fluid pressure in humans, and dilatation of the pial vessels in the cat. The following year, Aring *et al.* (120) noted that nicotinic acid caused an increase in the rate of cerebrospinal fluid displacement, occurring during a standardized sudden brief compression of the veins of the neck, and concluded that it caused an equivalent increase in intracranial blood flow. However, Loman, Rinkel and Myerson (121) administered the drug by the intravenous, intrabrachial and intracarotid routes, and recorded the following findings: (i) the cerebrospinal fluid pressure was not significantly altered, (ii) the calibre of the retinal vessels was unaltered, (iii) the cerebral bloodflow, using changes in the arteriovenous differences in oxygen content as an index, was only slightly increased, while the bloodflow in the arm was moderately to markedly increased, (iv) nicotinic acid shortened the Raynaud-like response produced by epinephrine when both drugs were injected into the brachial artery.

The latter results are supported by those of a more recent study. Using the nitrous oxide method for measuring cerebral bloodflow, Scheinberg (122) in 1950 investigated the effects of nicotinic acid in 20 subjects. He concluded that "intravenous nicotinic acid in flushing doses produces no change in cerebral blood flow, arteriovenous oxygen and glucose difference, oxygen and glucose consumption, or vascular resistance". The comment may be made, however, that the findings as initially recorded would tend to indicate a considerable increase in cerebral blood flow in two cases, and a diminution in arteriovenous oxygen difference in four cases, but that the author attributed these findings to contamination of the internal jugular blood by extracerebral blood.

Opposed to the results of the latter two investigations, and in support of the earlier studies of Moore (119) and Aring *et al.* (120) are the findings of Furtado *et al.* (123), who investigated nicotinic acid and its derivatives for a number of years. In animals, they measured and photographed variations in calibre of the small vessels of the cortex and the retinal vessels, while in man they investigated the effects of intravenous injections on retinal vessels, ocular tension, C.S.F. pressure, blood pressure and skin temperature. They found that nicotinic acid and quinine nicotinate had a very marked vasodilating action on cerebral and retinal vessels, while nicotinic acid amide had not, except in very large doses. The characteristics of this vasodilatation were as follows: (i) it was more marked for the small vessels of the brain, particularly the arterioles, than for the large, (ii) the retinal vasodilatation was accompanied by cerebral vasodilatation, (iii) it could be obtained by retro-ocular injection of the nicotinic derivative, (iv) it was accompanied by a very moderate fall in blood pressure and a certain increase in C.S.F. pressure, (v) its action was transient, vessels returning to their previous calibre within 15 to 20 minutes. It was also found that, as compared with other substances tried out under the same conditions (acetylcholine, histamine, aminophylline, nitroglycerine), the cerebral vasodilating action of these nicotinic derivatives was much stronger and almost without repercussions on the general circulation.

The latter investigations are the most extensive in the literature, but in view of the conflicting experimental evidence it may still be questioned whether nicotinic acid causes cerebral vasodilatation, with increased cerebral blood flow, *in all instances*. It may well be that niacin is better able to effect vasodilatation in individuals with mild cerebral arteriosclerosis (with functional rather than structural constriction of the cerebral vessels) than in those with normal vessels.

In this connection, it may be mentioned that Scheinberg's 20 cases were all chosen at random from the wards of a general hospital, that the oldest member of the group was aged 60, and that none were reported to be showing psychotic symptoms.

Freyhan, Woodward and Kety (124), using the nitrous oxide technique, have made quantitative measurements of cerebral blood flow and metabolism in patients with organic psychoses of senility. They concluded that these psychoses of senility were associated with, and probably the result of a significant reduction in cerebral oxygen utilization, on the basis of an increased cerebrovascular resistance and its resultant significant reduction in blood flow through the brain. It would be interesting to compare the effects of nicotinic acid on cerebral blood flow and metabolism in a similar group of patients having psychoses of senility, with these effects of nicotinic acid in a group of normal controls.

Inferences as to the occurrence of vasodilatation in the psychoses of senility could also be made from a comparison of the clinical effects of niacin and niacinamide in such patients, it being agreed that the latter has no such effect.

(d) *Other Actions—Physical and Psychological*

For the sake of completeness two other possible actions of nicotinic acid may be recorded.

It has been suggested (83) that in some conditions niacin may act as a "physical alterative", and that the repeated pronounced peripheral vasodilatation may be compared with the effects of physiotherapy which in most of its applications also produces vasodilatation.

It is also noted that the pronounced vasodilatation often makes a strong impression on the patient, and it may therefore exert some effect by rendering the patient more receptive to suggestion by the therapist.

2. The Administration of Nicotinic Acid

The mode of administration of this drug, and the dosage, depend on whether it is being given prophylactically or therapeutically.

(a) *The Prophylactic Administration of Nicotinic Acid*

The average daily adult requirement of nicotinic acid is about 12 to 20 mgm. (15). The presence of this quantity in the diet is ensured by informed food selection and by food enrichment. In a recent evaluation of the enrichment programme in the United States, Sebrell (125) pointed out that in the 1920's and 1930's pellagra was the most serious deficiency disease in that country. For the past 25 years, however, the incidence of pellagra has shown a consistent downward trend. This is attributable in part to complex socio-economic factors, but also to a public health programme of nutritional education and enrichment. Enrichment of bread with niacin (and other nutrient essentials) was commenced on a voluntary basis in 1941, and made compulsory by Federal law from 1943 to 1946. Since this time more than half the States have passed laws making enrichment mandatory, and the programme has been largely continued on a voluntary basis in the remaining States.

In 1928, at the height of reported mortality in that country, there were approximately 6 deaths per 100,000 population from pellagra. By 1937, the year niacin was isolated and applied to the treatment of pellagra, the mortality was about 2·5 per 100,000. In 1943, two years after niacin-enriched foods appeared on the market, the rate was 1, and by 1950 it had dropped to 0·2 per 100,000 population. Mortality rates do not reflect the true health importance of pellagra (in a region of high prevalance, for example, at least 33 cases per death were found in 1917), but there has also been a corresponding reduction in the incidence of recognizable clinical pellagra reported from various centres. Even among chronic alcoholics, once commonly afflicted, clinical pellagra has become rare, in spite of the fact that there appears to have been no significant change in their economic status, alcoholic consumption, or eating habits, apart from the consumption of vitamin-enriched bread. Comparable declines have been noted in the incidence of both Wernicke's encephalopathy and the syndrome of "nicotinic acid deficiency encephalopathy" described by Jolliffe, which have also been attributed to the enrichment of bread and flour with thiamin and niacin respectively (126).

However, Sebrell recognizes that there remains the problem, the extent of which is uncertain, of borderline deficiencies of niacin and other nutrients. Such subclinical deficiencies are probably extremely common in alcoholism, senility and a number of other conditions—biological, psychological and/or social in origin. It has been suggested that some deficiency of niacin may well contribute to the production of the organic psychoses associated with senility (and alcoholism), and hence that administration of amounts in excess of the normal adult requirements may help to prevent or delay their onset. It is also necessary that the education of physicians shall make them aware of the great variety of functional and organic disorders in which vitamin requirements are increased (v. supra—section A, 2) so that they may prescribe adequate amounts of supplementary vitamins at such times.

(b) *The Therapeutic Administration of Nicotinic Acid in Psychiatric Disorders*

There are several aspects of the therapeutic administration of niacin that require consideration: (i) whether niacin is preferable to niacinamide or vice versa, (ii) whether other nutritional therapy should be administered concurrently in all cases, (iii) the route of administration, (iv) the size and frequency of dosage, (v) the duration of therapy.

(i) *Selection of niacin or niacinamide.* After taking an oral dose of 50 mgm. or more of nicotinic acid, particularly on an empty stomach, flushing of the face, neck and other parts of the body may occur within ten or twenty minutes. In larger doses, many patients complain of burning, itching, headache, palpitation, abdominal discomfort, or other subjective sensations resulting from vasodilatation. Niacinamide does not cause this vasodilatation, and may therefore be preferred when only the metabolic actions of the vitamin are required. Some authorities have stated that the use of niacinamide is always to be preferred to that of niacin. However, at least part of the therapeutic effect of niacin in some psychiatric disorders has been attributed to cerebral vasodilatation, with increased blood flow to the brain (v. supra). Hence, *in the present state of our knowledge regarding its actions in psychiatric disorders, it is probably advisable to use nicotinic acid rather than its amide in all but clear-cut deficiency states* (83).

(ii) *Administration of other nutritional agents concurrently with niacin.* It has been pointed out that pellagra may be precipitated by diets deficient in tryptophane (believed to be the precursor from which niacin is synthesized in the intestines), and is usually associated with a deficiency of one or more other vitamins, particularly thiamin and riboflavin. Consequently, for the adequate treatment of pellagra, it is usually recommended (10–12, 32, 46, 127) that, in addition to specific therapy with niacin or its amide, a diet should be prescribed that is rich in protein (as well as foods containing niacin), and whole vitamin B complex should also be administered.

Moreover, it has been remarked (13, 81) that large doses of a single vitamin, especially of the B group, may precipitate latent deficiencies of other vitamins, and so cause unpleasant side-effects. In view of these considerations, *when nicotinic acid is administered in psychiatric disorders, it is probably advisable to administer other supplementary vitamins (particularly whole vitamin B complex) together with a high protein diet if there is any possibility of nutritional deficiency, and perhaps in all instances.*

(iii) *The Route of Administration* selected depends partly on the severity of the disorder present and partly on the rationale for therapy with niacin. The substance may be administered either orally or parenterally, but the latter route is nowadays rarely considered necessary in cases of deficiency disease unless the condition of the patient is critical, as in delirium or coma. In such cases parenteral administration is adopted during the initial phases of treatment.

The intravenous route has also been used by a number of investigators for the purpose of effecting rapid vasodilatation. However, it is not wholly devoid of risk, an occasional severe reaction with collapse having been observed. In any event, marked vasodilatation can be obtained readily, conveniently, and as often as desired, by the oral administration of adequate doses, particularly on an empty stomach.

(iv) *Size and Frequency of Dosage.* Different schedules of dosage recommended vary greatly, and again depend partly on the severity of the disorder present and partly on the rationale for this form of therapy. In cases of pellagra, maximal dosage is prescribed initially, the total amount varying from 200 to 1,000 mgm. daily according to the severity of the condition, 500 mgm. being considered as usually effective. This total amount is frequently administered in divided doses (e.g. 50 or 100 mgm., from four to ten times a day) for the purpose of maintaining the blood level. All or a part of this amount may be given parenterally initially, but administration is usually oral, and dosage is gradually reduced over a period of several weeks. However, it is sometimes recommended that, even when the patient has apparently fully recovered, a maintenance dose of 50 to 150 mgm. orally per day should be continued for prolonged periods, and perhaps indefinitely in senile patients.

Doses prescribed in order to effect vasodilatation have often been larger but less frequent—individual doses recorded being as high as 400 mgm. intravenously or 900 mgm. orally, but sometimes being administered only every second day or at even longer intervals. However, a number of physicians have prescribed for this purpose several large doses daily by mouth. One such regime, which incidentally provides a convenient compromise between the divided doses suggested in deficiency disease and the relatively large doses desired for marked vasodilatation, is the administration of 300 mgm. three times daily ½ to 1 hour before meals.

(v) *The Duration of Therapy* depends again partly on the rationale, but also on the patient's response to therapy. In pellagra of acute onset there is usually a fairly rapid response over a period of a few days, and sometimes even a dramatic improvement within a few hours, but in cases of longer duration the response tends to be much slower and the recovery of function less complete. Probably a considerable proportion of the final recovery of function will have occurred within a week, and most within a month, of the commencement of maximal dosage. However, it should be noted that a three months' trial of therapy has been recommended in psychoneurotic syndromes believed due to mild niacin deficiency.

Similar responses to therapy have been observed in other organic mental disorders of less certain aetiology, in which niacin may have been acting by virtue of its metabolic properties or by means of vasodilatation or both. In cases in which the rationale of niacin therapy has been vasodilatation alone, it has been a common practice to place the patient on a therapeutic trial of about three or four weeks duration.

3. CONCLUSION: RATIONALE FOR ADMINISTRATION OF NICOTINIC ACID IN PSYCHIATRIC DISORDERS

Nicotinic acid has been selected for consideration from amongst the other members of the vitamin B complex with full recognition of a number of factors that might argue against such special attention, including the following: (i) that there is an intimate functional interrelationship (biochemical and physiological) between the various members of the vitamin B complex, (ii) that deficiency of one member of the vitamin B complex is commonly associated with varying degrees of deficiency of the other members, (iii) that psychiatric manifestations of deficiency of one such member of the B complex may be very similar to those caused by deficiency of another member, (iv) that administration of one member of the vitamin B complex may precipitate latent deficiencies of other members, (v) that for all these reasons, administration of niacin should be accompanied by administration of other members of the vitamin B complex (though not necessarily in equivalent dosage).

Nevertheless, the literature on niacin specifically has appeared to merit individual consideration, for several reasons: (i) mild degrees of niacin and other vitamin deficiencies are probably much more common than generally realized, (ii) the first signs of niacin deficiency may be the development of psychiatric manifestations, (iii) the psychiatric manifestations of niacin deficiency may possibly be more pronounced than those of equivalent degrees of deficiency of other members of the vitamin B complex, (iv) if niacin deficiency remains uncorrected, these psychiatric manifestations may become irreversible, (v) improvement in certain psychiatric disorders following administration of niacin is attributed to vasodilatation, an action not possessed by niacinamide or other members of the vitamin B complex.

Finally, the psychiatric disorders in which nicotinic acid has been reported to effect improvement are tabulated below, according to the postulated rationale for such improvement:

(a) *Psychiatric disorders attributed wholly to nicotinic acid deficiency*

- (i) Pellagra, the characteristic mental changes progressing as follows:

$$\text{Depression} \xrightleftharpoons{\text{reversible}} \text{Delirium} \xrightarrow{\text{irreversible}} \text{Dementia.}$$

- (ii) Pellagra sine pellagra, mental changes occurring in the absence of physical changes (these mental changes consisting in mild cases of psychoneurotic syndromes).
- (iii) Nicotinic acid deficiency encephalopathy, with specific neurological manifestations.

(b) *Psychiatric disorders with possible relative or associated deficiency of nicotinic acid, but in which part of the therapeutic effect of nicotinic acid has also been attributed to mass action and/or vasodilatation*

- (i) Atypical organic psychoses associated with malnutrition
- (ii) Organic psychoses associated with alcoholism
- (iii) Organic psychoses associated with senescence and senility.

(c) *Psychiatric disorders apparently unrelated to nutritional deficiency, in which the therapeutic effect of nicotinic acid has usually been attributed to vasodilatation*

- (i) Organic brain dysfunction following cerebral trauma, and hypoxic episodes.
- (ii) Organic brain dysfunction following somatic psychiatric therapies (e.g. E.C.T., prolonged insulin coma, lobotomy).
- (iii) Apparently functional depressive and anxiety reactions.

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DIFFERENTIAL CEREBRAL ELECTROSTIMULATION

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(Received 8 May, 1954)

CEREBRAL electrostimulation of subconvulsive intensity causes a pronounced increase in the concentration of adrenaline-like substances in the blood (Weil-Malherbe and Bone, 1952b). This effect is presumed to be due to a central action of the current, since these investigators were unable to demonstrate any rise when both electrodes were placed on the same side of the head. The current which was used in these experiments consisted of brief rectangular impulses with a repetition rate of 100 pulses per second (Montagu, 1953). Recently, while experimenting with shorter pulses at correspondingly higher repetition rates, the author observed that the motor response diminished as the frequency was raised, the peak and average current levels remaining constant. This effect, which appeared to be due to the progressive abbreviation of the pulses to the point at which they ceased to be effective motor stimuli, suggested that these conditions might be advantageous in electrostimulation therapy, provided that the autonomic effects were not equally impaired. Firstly, however, it was necessary to determine whether the diminution in the motor effects at the higher frequencies was part of a generalized reduction in the efficiency of cerebral stimulation or whether there was a differential response. Accordingly, with the assistance of Dr. Weil-Malherbe, the blood adrenaline level has been studied in relation to the different conditions of stimulation. The results of this investigation are contained in the present report.

ELECTROTECHNIQUES

Several types of current have been used in subconvulsive stimulation therapy: faradic current (Berkwitz, 1940), alternating current (Riboli and Mancini, 1948), the Reiter current (Hirschfeld, 1950; Alexander, 1950, 1953), and Liberson's Brief Stimuli (Hirschfeld and Bell, 1951; Montagu, 1953). In general, the frequency of stimulation has been low, ranging from 28 pulses per second, the basic frequency of the Reiter current (Alexander, 1953), to 120 p.p.s. with brief rectangular impulses (Hirschfeld and Bell, 1951), although Berkwitz (1952) has recently used a faradic current at a repetition rate of about 300–400 p.p.s. In convulsive therapy, Cossa *et al.* (1948), employing "square waves" with a pulse/interval ratio of unity, used frequencies up to 600 p.p.s., while Hirschfeld and Bell (1951) have given up to 500 brief stimuli per second. The latter workers were studying the clinical effects of varying the parameters of stimulation, and it seemed to them that low frequencies of about 20 p.p.s. with a pulse duration of 1·5 milliseconds produced a greater autonomic response than shorter pulses at higher repetition rates. However, the autonomic effects have not been previously measured in relation to different conditions of cerebral stimulation.

Of the various types of electrical stimulus the rectangular form possesses certain advantages, namely:

(1) On *scientific* grounds it is accurately measurable in all dimensions: pulse duration, pulse interval, and peak current.

(2) Its adoption has been proposed on *physiological* grounds by Liberson (1945), who suggested that the pulse duration should be compatible with the chronaxie, and the interval with the refractory period, of the neurones.

APPARATUS

The current consisted of brief, unidirectional, rectangular impulses ("square waves"), which were obtained from a small high-tension battery by means of a commutator-interrupter, i.e. it was an "interrupted galvanic" current in the true sense of the term. The apparatus was similar to that which was used by Leduc (1903) at the beginning of the century.

The circuit diagram of the stimulator is shown in Fig. 1. The central feature is an electric motor, the armature of which carries two commutators, one at each end. One of the commutators (C_1) is connected with the armature windings and is used to drive the motor from the mains supply. A variable resistance (R_1) in this circuit enables the speed of rotation to be controlled. The other commutator (C_2) is isolated from the armature and is used to make and break a secondary circuit. It consists of two narrow metal segments, which are diametrically opposed but connected together. Two brushes, in contact with the commutator, are also diametrically opposed, so that the secondary circuit is made during a few degrees in each half-cycle of the commutator. This results in a series of brief "square waves" with a frequency equal to double the speed of the motor. The secondary circuit supplies the patient from a small 67½ volt battery and is completed, in series, by a switch, a rheostat (R_2) for controlling the current, and a milliammeter.

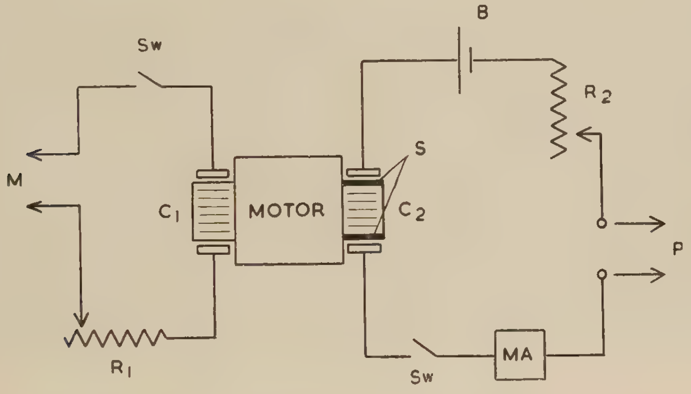

FIG. 1.—Circuit diagram of the stimulator. B—67½ volt battery. C_1 and C_2—commutators. M—mains. MA—milliammeter. P—patient. R_1 and R_2—rheostats. S—metal segments (connected together). Sw—switch.

A system of this type enjoys some advantages, and a few disadvantages, when compared with the more complex electronic circuits:

A. Advantages

(1) *Simplicity.* The apparatus is cheap, robust, and compact. The last of these points is illustrated photographically in Fig. 2.

(2) *Safety.* This derives from the mutual isolation of the primary and secondary circuits, the mains serving no other function than that of driving the motor.

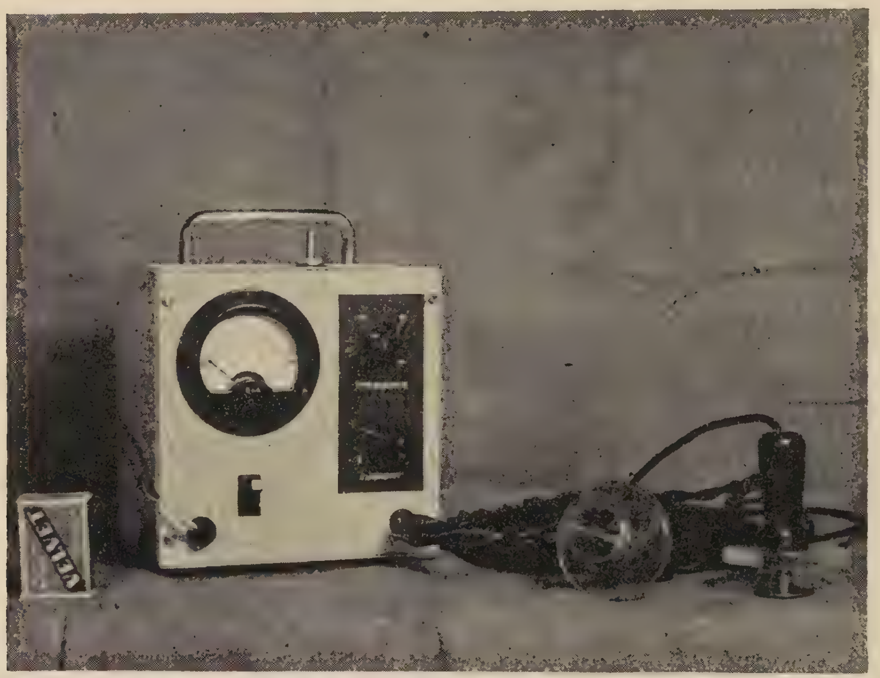

FIG. 2.—Photograph of the stimulator and electrodes. The size is shown by comparison with a match-box.

(3) *Variable frequency* may be easily obtained, within moderate limits, by a simple control of the speed of the motor.

(4) *Constant quantity output* which is independent of frequency. The relative values of pulse duration and pulse interval are determined by the design of the commutator and the position of the brushes. Leduc (1903) used an adjustable brush whereby the pulse duration could be varied at the expense of the interval, but in the present instance the ratio was fixed. The absolute values, on the other hand, depend upon the speed of the motor. However, since any alteration in the speed of rotation is accompanied by an inversely proportional change in both pulse and interval (see Fig. 3), the average output remains constant, for any given peak current, at all frequencies. This condition was required for the present investigation.

B. Disadvantages

The disadvantages of a commutator-interrupter relate, principally, to the accuracy and constancy of the electrical characteristics.

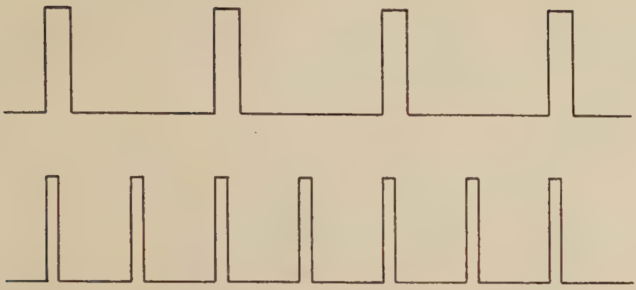

FIG. 3.—Diagram of the wave-form (not to scale), showing the effect of doubling the frequency.

(1) *Wave-form.* This is liable to distortion by the occurrence of sparking at the brushes, a condition which is manifested, oscillographically, in spiked or fuzzy contours. A single impulse from the present apparatus is illustrated in Fig. 4, which demonstrates its freedom from this effect.

(2) *Pulse duration.* The present system produces two pulses during each revolution of the motor. Alternate pulses will therefore differ in duration if the brushes or the segments are not both in exact diametrical opposition. This is illustrated in Fig. 5, which shows two consecutive pulses superimposed, as indicated by the double trailing edge. The difference in duration between the two pulses amounts to 10 per cent. of the mean duration.

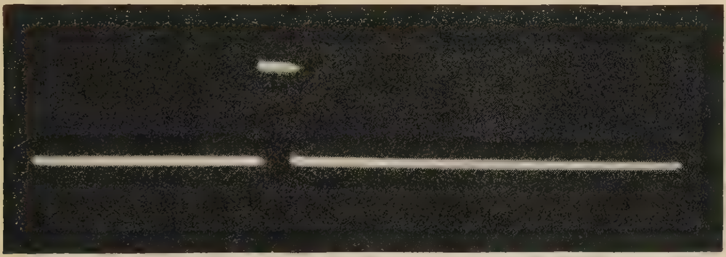

FIG. 4.—Oscillographic trace of a single pulse.

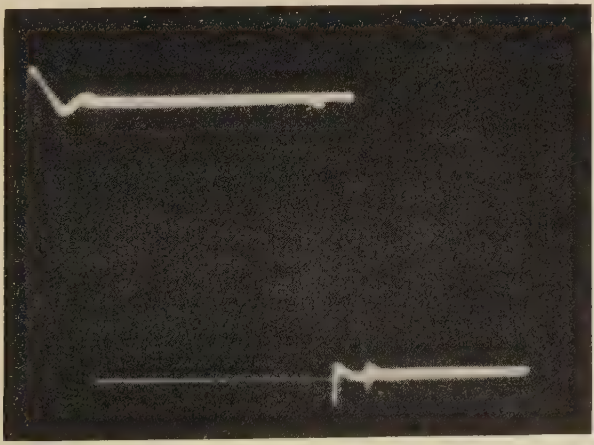

FIG. 5.—Triggered and expanded trace showing the alternate pulses superimposed, as indicated by the two trailing edges. The spot, at the left end of the base line, has been blanked out.

(3) *Frequency*. This is determined by the speed of the motor, which in turn varies with the input voltage and with sundry frictional losses. These factors introduce a liability to shift of frequency over a certain range, but this occurs proportionately at all levels.

By oscillographic methods the pulse/interval ratio of the present system was found to be almost exactly 1 : 24, while the maximum frequency, at mains voltage, was 500 pulses per second. Under these conditions the durations of pulse and interval at various available frequencies are, by calculation, as follows:

Frequency p.p.s.	Pulse Duration μsec.	Pulse Interval msec.
100	400	9·6
200	200	4·8
300	133	3·2
400	100	2·4
500	80	1·9

The ratio of peak current, determined on the oscillograph, to average output, as recorded by the milliammeter, was, however, only 20 : 1, compared with the cycle/pulse ratio of 25 : 1. This discrepancy was the result of a combination of slight errors from several sources, e.g. wave-form, meter, etc. Accordingly, with a peak current of 100 mA. the average output was 5 mA. This remained absolutely constant over the entire range of frequencies. Owing to this small consumption one miniature 67½ volt battery survived continuous use for six months, during which time it delivered approximately 400 treatments each of five minutes' duration. The circuit shown in Fig. 1 has an approximately constant voltage characteristic, so that good electrode contacts are necessary; otherwise an adequate current cannot flow. Nevertheless, in the following experiments the current, not the voltage, was recorded, and the tendency to variation was found to be negligible once the required level had been attained.

METHODS

The subjects of this investigation were 15 males suffering from anxiety states who had been admitted to Roffey Park Rehabilitation Centre. All were receiving treatment by subconvulsive electrostimulation. The electrodes were circular, 3 cm. in diameter, and were applied bitemporally about one inch above the attachments of the pinnae. After preliminary anaesthesia with thiopentone, and application of the electrodes, the current was switched on and was raised rapidly to 4 mA. (80 mA. peaks). This was usually the highest intensity which could be maintained without causing undue respiratory embarrassment at the lower frequencies. On one exceptional occasion it became apparent immediately that this current would not be endured, and the level was reduced to 3½ mA. (70 mA. peaks). On all other occasions the initial apnoea was transient and the higher intensity was maintained for the duration of the experiment.

Samples of blood were collected by withdrawing 15 ml. into 5 ml. of a special fluoride-thiosulphate solution (Weil-Malherbe and Bone, 1952a). An initial specimen was obtained immediately before the injection of thiopentone, and a second one was taken about a minute after the injection. A number of specimens were then collected at intervals during stimulation at various frequencies, the intensity remaining unaltered throughout. In every instance at least 1½ minutes was allowed to elapse after a change of frequency before the withdrawal of the next sample was begun. A final specimen was taken one to two minutes after the current was switched off. The blood samples were centrifuged, and the plasma adrenaline and noradrenaline concentrations were estimated at Runwell Hospital by the method of Weil-Malherbe and Bone (1952a, 1953).

MOTOR EFFECTS

Initial trials with the present apparatus began with frequencies of 100–200 p.p.s. (pulse durations of 400–200 μsec. respectively) and with peak currents of 60–80 mA. These conditions are similar to those which had been used previously, viz. 100 p.p.s. with a pulse duration of 300 μsec. (Montagu, 1953), and similar motor effects were obtained. These included spasm of the facial muscles, tonic contractions of the arms and, to a lesser extent, of the legs, respiratory embarrassment above a certain intensity of current, and pronounced stimulation of respiration below that level. The frequency was then steadily raised to 500 p.p.s. at the same peak current, the pulse duration diminishing correspondingly to 80 μsec. This resulted in progressive relaxation; the arms fell to the patient's side, and the respirations lost their forced character and assumed a normal rhythm. During this process the muscles of the shoulder girdle were the first to lose their tonus, followed in sequence by those of the upper arm, forearm, and hand. Although some change was seen throughout the entire range of frequencies, the most noticeable alteration occurred in the vicinity of 300 p.p.s. At 400 p.p.s. the patient already appeared relaxed. When the frequency was reduced, the effects were reversed. At the lower end of the scale, down to 100 p.p.s. and below, the tonus became more intense and more generalized, the facial contortion steadily increased, and the respirations assumed the alarming character of shallow, jerky grunts. This cycle of events could be produced and reversed as often as the frequency was raised and lowered.

SENSORY EFFECTS

Cerebral stimulation at low frequencies is known to be antagonistic to barbiturate narcosis (Hirschfeld, 1950; Robie, 1950). It reduces, to about one half, the normal duration of anaesthesia following intravenous induction. The patient, however, usually relapses into stupor when the current is discontinued. Within five minutes of receiving 0·5 gm. of thiopentone intravenously most patients, under continuous stimulation at 200 p.p.s. or below, make a purposive response by raising their hands to the electrodes. Continued stimulation may be experienced as a most unpleasant vibration within the head. If, however, the frequency is raised to 500 p.p.s. as soon as a response is elicited, the hands return to the side, and the patient accepts the current at the same intensity for a period which may be as long as the initial interval. A reduction of frequency during this time again brings the hands up to the electrodes, when an increase will once more abolish the response. When, on the other hand, stimulation is maintained at 500 p.p.s., the patient may ultimately obey a simple request or even reply to a question before making any defensive movements, and if, at this point, the current is discontinued, he frequently denies any painful experience. Others describe a sensation of vibration which they do not, in general, regard as unpleasant. Although, however, the higher frequencies appear to cause less intense sensory stimulation than the lower ones, it has not been found practicable to dispense with the preliminary anaesthesia.

AUTONOMIC EFFECTS

The blood adrenaline and noradrenaline concentrations were estimated as indices of sympathetic activity. It was found, however, that in the present series of experiments the noradrenaline level showed only slight and inconsistent variations as a result of the stimulation. This observation has been subsequently explained by Weil-Malherbe (1954), who has demonstrated that pentothal anaesthesia prevents the increase in noradrenaline which normally occurs after E.C.T. Accordingly, only the adrenaline results will be considered.

In the first three cases the effects of "high" and of "low" frequencies were measured in separate experiments. In the morning the patient was treated by stimulation at 200 p.p.s., and blood samples were taken before and after the induction of anaesthesia, 3 minutes after the onset of stimulation, and a minute after switching off. In the afternoon of the same day the procedure was repeated with stimulation at 500 p.p.s. but under otherwise identical conditions of anaesthesia, timing, and intensity. The results of these experiments are presented in Fig. 6. This shows that on each occasion the stimulation caused an increase in circulating adrenaline, which was more pronounced in response to the higher frequency in all three cases. The brisk initial fall in adrenaline following pentothal has been previously reported by Weil-Malherbe and Bone (1952a) and was a constant feature of the present experiments.

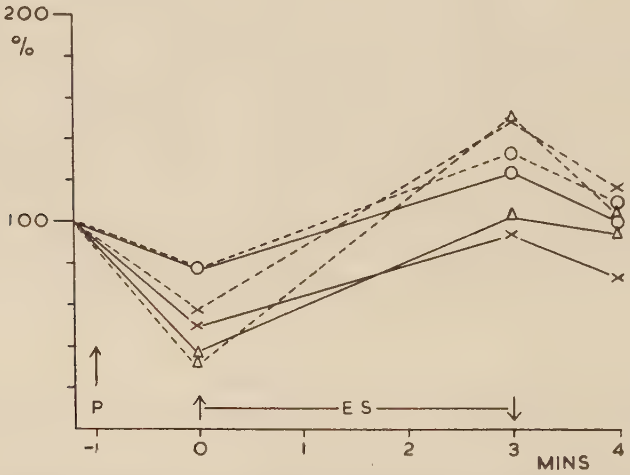

FIG. 6.—The effects of stimulation at 200 p.p.s. (solid lines) and at 500 p.p.s. (broken lines) on the blood adrenaline in 3 patients. Adrenaline concentrations are expressed as percentages of the initial levels. P denotes injection of pentothal.

This method of comparing the effects of different electrical conditions appeared to be unnecessarily laborious; it seemed preferable to study them consecutively in one experiment. Three cases were therefore stimulated at 200 p.p.s. for 3 minutes and then at 500 p.p.s. for a further 3 minutes, blood samples being taken at the end of each period. The results are presented in Fig. 7, which shows, in each case, an increase in blood adrenaline in response to the lower frequency, followed by an additional, and almost equal, increase after the rise in frequency. These results, however, do not take into account the effect of the waning anaesthesia, nor the fact that a minimal period must elapse before the

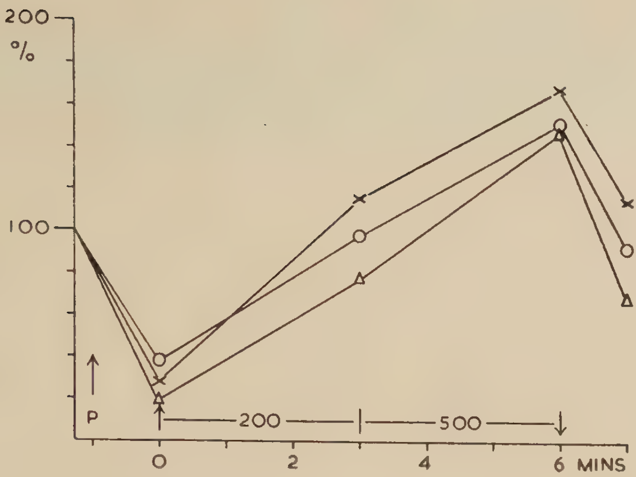

FIG. 7.—The effect of consecutive stimulation at 200 p.p.s. and at 500 p.p.s. on the blood adrenaline in 3 patients. Adrenaline concentrations are expressed as percentages of the initial levels. P denotes injection of pentothal.

adrenaline concentration reaches its new level. Both of these factors could contribute to a continued increase in adrenaline during the second part of the stimulation. To test the influence of these factors a third group of three subjects was investigated in the same manner as the second group, but the frequencies applied in the reverse order. The results of these experiments are shown in Fig. 8. Here again it can be seen that the higher frequency produced

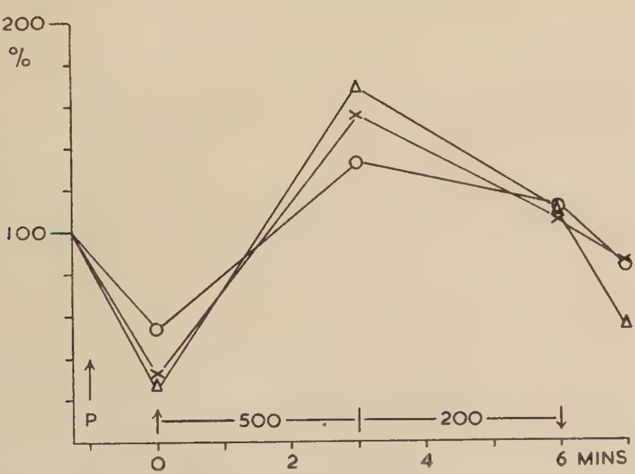

FIG. 8.—The effect of consecutive stimulation at 500 p.p.s. and at 200 p.p.s. on the blood adrenaline in 3 patients. Adrenaline concentrations are expressed as percentages of the initial levels. P denotes injection of pentothal.

the greater response, as evidenced by a fall in the blood adrenaline during the second half of each experiment.

The effects observed in the above nine cases are presented collectively in

Fig. 9.* In every instance stimulation at 500 p.p.s. caused a greater liberation of adrenaline than a repetition rate of 200 p.p.s., the peak and average currents remaining constant. To obtain further information concerning the nature of the adrenaline-frequency relationship six more experiments were performed with the inclusion of the intermediate steps of 300 and 400 p.p.s. In three cases all four frequencies were used consecutively in different orders, blood samples being taken $1\frac{1}{2}$–2 minutes after each change of frequency. In a fourth case the three higher frequencies were applied in descending order before the patient started to "object" to the current, and in the last two cases the two highest frequencies alone were used in reverse orders. The results of these experiments are demonstrated in Fig. 10.* This shows that, with one exception, each

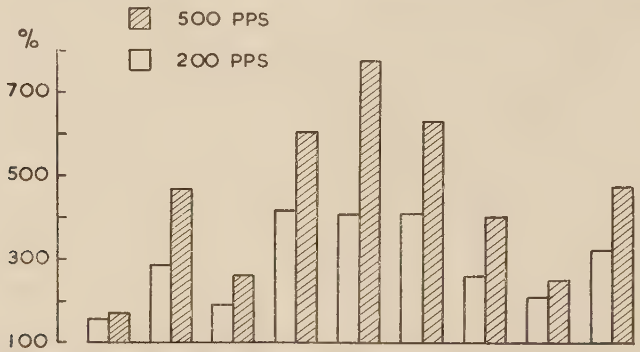

FIG. 9.—Block diagram comparing the effects of stimulation at 200 p.p.s. and at 500 p.p.s. on the blood adrenaline in 9 patients. The scale represents adrenaline concentration expressed as a percentage of the basal level after induction of anaesthesia.

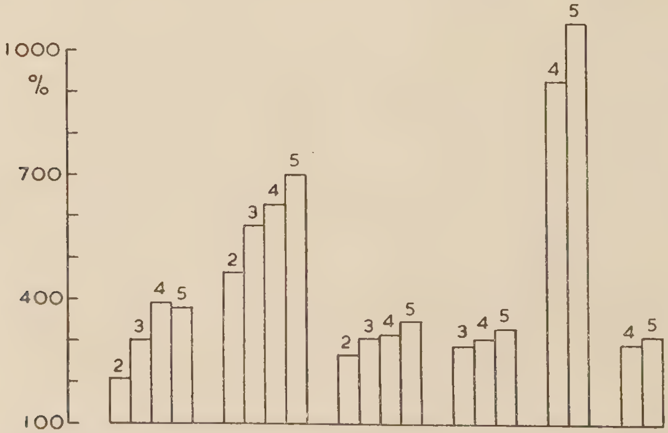

FIG. 10.—Block diagram comparing the effects of stimulation at various frequencies on the blood adrenaline in 6 patients. The figure above each column denotes the frequency in p.p.s. divided by 100. The scale represents adrenaline concentration expressed as a percentage of the basal level after induction of anaesthesia.

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* In Figs. 9 and 10 the response to stimulation appears to vary greatly from case to case. This impression is deceptive. The adrenaline levels are expressed as percentages of the basal levels *after* induction of anaesthesia, so that the diagrams also reflect variations in response to the anaesthetic. In fact, the base lines ranged from 0·20 to 1·58 μg. adrenaline per litre, which largely accounts for the great differences in percentage increase.

successive rise in frequency caused an additional increase in circulating adrenaline and, conversely, that each reduction in frequency resulted in a fall. In the exceptional case (shown on the left in Fig. 10) there was a slight decrease in adrenaline when the frequency was raised from 400 p.p.s. to 500 p.p.s. The nature of the relationship between frequency and blood adrenaline is particularly well illustrated in one experiment of this series, which is reproduced graphically in Fig. 11.

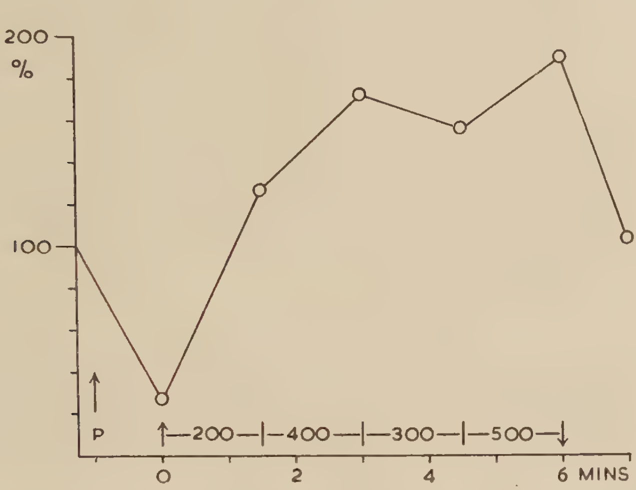

FIG. 11.—The effect of consecutive stimulation at four different frequencies (expressed in p.p.s.) on the blood adrenaline. Adrenaline concentrations are expressed as percentages of the initial level. P denotes injection of pentothal.

DISCUSSION

The results have shown that the sensory and motor effects diminished, while the sympathetic response increased, when the frequency of stimulation was raised from 200 to 500 p.p.s. at the expense of the pulse duration (peak and average currents constant). This observation conflicts with the impression of Hirschfeld and Bell (1951) that the autonomic nervous system responds better to lower frequencies with longer pulses.

There are two possible explanations for the present findings, namely:

(1) That the different frequency responses are due to intrinsic differences in the sensory, motor, and sympathetic systems.

(2) That at higher frequencies there is less spread of the current with its consequent localization to the inter-electrode line. Since the electrode placement has been chosen so that the inter-electrode line passes through the diencephalon (Hirschfeld, 1950), any restriction of the path of the current would intensify diencephalic stimulation and would reduce the effects on remoter structures.

The second of these postulated mechanisms can easily be put to the test by moving the electrodes to some indifferent area. If the assumption is correct and the current becomes more localized at the higher frequencies, there will be less stimulation of the diencephalon under these conditions, so that the blood adrenaline–frequency relationship will be the converse of that which has been previously found. This test has, in fact, been done. Two subjects were re-investigated during consecutive stimulation at 200 and at 500 p.p.s. but with the electrodes placed high up on the frontal regions. The results are presented in Fig. 12, which shows that the adrenaline responses, although less pronounced, are qualitatively similar to those which were obtained with the normal electrode placement. There is, therefore, no evidence of any change in the distribution of the current under the different conditions of stimulation.

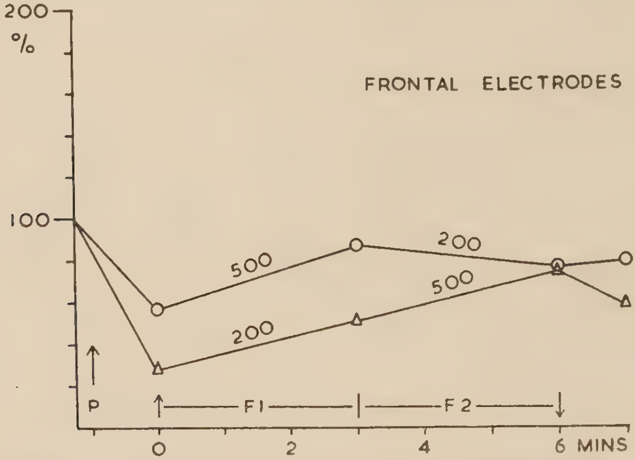

FIG. 12.—The effect of consecutive stimulation at different frequencies through high frontal electrodes on the blood adrenaline in 2 patients. The figures above the curves denote the frequencies F_1 and F_2 in p.p.s. P denotes injection of pentothal.

The explanation for the differential response to the higher frequencies is most likely to be found in the relative chronaxies and refractory periods of the different types of neurone, but little supporting evidence can be adduced from the present results. Although, for the sake of convenience, the electrical conditions have been expressed throughout in terms of the frequency, this term, in fact, has little meaning when applied to other than sinusoidal currents. It is merely an expression of the combined pulse duration and interval, which are the determining factors. As Liberson (1945) has emphasized, the pulse duration should be compatible with the chronaxie, and the interval with the refractory period, of the neurones. In the present experiments the pulse duration diminished from 400 μsec. to 80 μsec. as the frequency rose from 100 to 500 p.p.s. During this process the most noticeable change in the motor response occurred in the vicinity of 300 p.p.s., at which point the pulse duration was about 130 μsec. It is interesting to note that this figure is of the same order as the chronaxie of the motor nerves (Best and Taylor, 1950), although the significance of the agreement is doubtful since the intensity of stimulation relative to the rheobase is unknown. The issue is further complicated by the effects of summation and facilitation. Of greater significance is the fact that the proximal muscles of the arms were the first, the distal muscles the last, to lose their tonus as the pulse duration diminished. This effect is in conformity with the observations of Wyss and Obrador (1937), who found that the chronaxie of the motor cortex for distal movements was less than that for proximal movements. The available evidence is therefore compatible with the suggested explanation of the results, but more definite conclusions cannot be drawn from the present data. However, on the assumption that the explanation is correct, the differential response to the briefer pulses indicates that the sympathetic centres have a chronaxie that is considerably shorter than those of the sensory and motor structures.

The increasing sympathetic response at higher frequencies of stimulation showed no signs of reaching a peak in the present experiments, except in one case. An attempt was made to boost the speed of the motor by raising the input voltage, and in this way the output frequency was increased to nearly 1,000 p.p.s. However, it was considered that the motor was unlikely to stand up to such high speeds for long, and so the attempt to extend the frequency range was abandoned. This was not the only limitation of the present apparatus. As mentioned earlier, it was not anyway subject to great constancy in respect of the frequency. Furthermore, the pulse/interval ratio was invariable, so that the results obtained are applicable to only one particular set of conditions. In consequence, although the present experiments have demonstrated a differential response, it has not been possible to measure the full extent of this phenomenon nor to determine the optimal conditions for sympathetic stimulation. A more versatile apparatus is required for these studies.

SUMMARY

The motor, sensory, and sympathetic effects of sub-convulsive electrotherapy have been studied in relation to different frequencies of stimulation. The blood adrenaline and noradrenaline concentrations were used as indices of sympathetic activity. Electrostimulation was performed under pentothal anaesthesia.

The current consisted of brief, unidirectional, rectangular impulses, which were produced by means of a commutator-interrupter. The pulse/interval ratio was constant, so that any change in frequency was accompanied by an inversely proportional change in both pulse duration and interval. Hence, at any given peak current the average output remained the same at all frequencies. The frequency was continuously variable from 100 to 500 pulses per second, corresponding to a pulse duration of 400 to 80 microseconds respectively. The electrodes were applied bitemporally just above each ear.

The results were as follows:

(1) The motor, sensory, and respiratory effects of the current diminished progressively as the frequency was raised.

(2) The output of adrenaline increased progressively as the frequency was raised.

(3) The circulating noradrenaline showed only slight and inconsistent variations. It is believed that the pentothal prevented the changes which otherwise would probably have occurred.

It was considered that these effects might be caused by an increased localization of the current at the higher frequencies. However, this possibility was eliminated by moving the electrodes to an indifferent area away from the diencephalon, when the adrenaline-frequency response was found to remain qualitatively unchanged. It was concluded that the effects were probably due to differences in chronaxie and refractory period in the different types of neurone.

ACKNOWLEDGMENTS

An acknowledgment is due to the Physician Superintendent, Dr. R. Ström-Olsen, for much advice and helpful criticism. To Dr. H. Weil-Malherbe I wish to repeat my thanks for his co-operation, without which these experiments could not have been performed. I am also indebted to Dr. L. S. Davies, Deputy Director of Roffey Park Rehabilitation Centre, for providing the clinical material. This was drawn from the subjects of a therapeutic investigation in which we are jointly concerned.

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THE DIFFERENTIAL EFFECT OF CORTISONE AND OF A.C.T.H. ON MOOD

By

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It is evident from many reports published in the last four years that psychological changes can occur during the treatment of physical illness by Cortisone and corticotrophin (A.C.T.H.). There is no doubt, too, that similar mental symptoms have been occasioned by giving either of these agents in therapeutic doses. It is perhaps for this reason that most writers have not distinguished between them in this respect. Thus, the mild mood changes that often occur, and the relatively rare psychotic reactions are usually spoken of as complications of A.C.T.H. *or* Cortisone therapy. This implies that, in the individual case, these substances would be equivalent in their influence on the mental state; yet there are grounds for suspecting otherwise. The aetiology of these psychological reactions remains obscure, so that any evidence which serves to differentiate the psychiatric side-effects of the two drugs would be of interest.

The few writers who have explicitly considered this aspect are not in close agreement. Hench and his colleagues (1950) in an early report on the treatment of patients with rheumatoid arthritis concluded that the "euphorigenic" effect of Cortisone was greater than that of A.C.T.H. This finding has not been corroborated by later writers. Irons and his colleagues (1951) found that all of their patients with collagen disease or chronic dermatoses treated with either drug experienced a sense of wellbeing at some stage, whereas only those given A.C.T.H. exhibited abnormal mental changes; these included depressive, hypomanic and schizophrenic episodes which did not occur when Cortisone was given subsequently.

In a psychiatric study (Lidz *et al.*, 1952) of 15 patients, most of whom were asthmatics, Cortisone was thought to have less euphoriant effect than A.C.T.H. The authors could not attribute this difference entirely to the greater relief from asthmatic symptoms provided by A.C.T.H. Goolker and Schein (1953) in a detailed psychiatric report on 80 patients treated for various physical conditions were unable to gain more than an impression that A.C.T.H. is "more likely to be associated with psychic phenomena". Other psychiatric observers (Rome and Braceland, 1952; Brody, 1952; Glaser, 1953; Rees, 1953) have been, in the main, silent on this point, but occasional hints of a differential effect have been given. Clark and his colleagues (1952), for example, noted wit interest that two of their patients in whom mental symptoms occurred during or immediately after A.C.T.H. therapy; had no recurrence of this disturbance during subsequent high dosage with Cortisone. Findings of this kind, however, have so often been apparently cancelled by others of similar sequence but with the reverse order of drugs, that the lack of emphasis accorded them is not surprising.

The following report concerns a young woman with psoriasis arthropathica in whom mood variations occurred during treatment with Cortisone and A.C.T.H. Her psychological changes will be considered in relation to the effects of these agents on her physical disease and her adrenocortical function.

CASE HISTORY

Miss P.G., aged 24.

Family History. Mother has familial tremor of hands and head. Father died when patient was aged 7: cancer of the bowel. The patient is the ninth of ten siblings: all are healthy except a brother who died aged 22 after an illness in which "his backbone turned to chalk". No other relevant physical illness or mental symptoms.

Personal History. At birth (1927) and during infancy her development was normal. She was a quiet child, who kept apart from her siblings and clung to her father. Little is known of her scholastic attainment, but at that age she was friendless and solitary.

When aged 14 she started work as a factory machinist, and had remained in her last job for 6 years, doing semi-skilled work. She lived at home with her mother and two unmarried siblings.

Menarche aged 14. Menses had been regular, 5/28, apart from amenorrhoea during chrysotherapy in 1947, and from December, 1951, until May, 1952, during a severe exacerbation of her illness. She had had only brief friendships with boys, and had shown little interest in sex or marriage.

Apart from herpes zoster at 8 years old, her physical health had been good before the onset of psoriasis.

Personality. Since early childhood she had been the "odd man out" in her family. She was taciturn and undemonstrative, with a preference for solitude and indolence. She was aloof and humourless and regarded as "moody", sullen and over-critical. She was unusual, too, in being very clean, tidy and orderly; she was quick to be angry if her belongings were moved out of place. She had no recreational interests apart from the cinema.

Present Illness—Physical. Psoriasis started in 1942 when she was 14, about 3 weeks before her first menstrual period. Until 1944 she was under the care of St. Thomas's Hospital and received topical therapy both in hospital and as an out-patient. Her scalp was never cleared, but a partial remission continued until 1947 when she suffered a severe relapse involving her face for the first time. At about this time the first symptoms of *Arthritis* began. This was confined to her feet. A course of gold injections and physiotherapy left her with only stiffness in the feet and a scaling scalp. Another psoriatic relapse occurred in 1949 without any further joint symptoms; but in the spring of 1951 she developed painful joint swellings, which were immediately followed by an exacerbation of psoriasis; this had spread to cover her entire body by December, 1951. Arthritic symptoms had subsided by then, but she was surprised to find early in the next year that movement of her shoulders was so impaired that she was unable to raise her arms above her head. Her finger and toe nails had been affected by psoriatic pitting and subungual thickening for 4 years. In spite of severe skin eruptions and painful joints she was able to remain at work until March, 1952, two weeks before she first attended the out-patient department of the Maudsley Hospital.

Present Illness—Mental. A change in her mood and behaviour was first noticed a few months before arthritic symptoms began in 1947. She became more seclusive and irritable and had brief spells of unaccountable weeping. During the next three years this tendency became more pronounced, and when either skin or joint symptoms were bad she was often manifestly depressed. In the past year depressive symptoms had seldom lifted, she was usually apathetic and morose; her irritability made her almost unapproachable. She had never expressed either suicidal or other frankly morbid ideas, but for some months she had been preoccupied with the fear of becoming a cripple.

In April and May, 1952, she was seen by Dr. Denis Leigh at the out-patient department on six occasions. Treatment consisted of brief interviews in which she was given strong encouragement and reassurance; also "mist. gent. acid." thrice daily. During this time, psoriatic lesions cleared rapidly from her face and trunk, and there was considerable improvement of her skin elsewhere. Her joint symptoms showed little change. Her affective symptoms improved appreciably. She was able to smile and talk more freely at hospital and was less gloomy and irritable at home.

On 23 July, 1952, she was admitted to the Maudsley Hospital under the care of Professor Aubrey Lewis.

On Examination—Physical. She was a tall, plump young woman of athletic habitus, with dark hair of normal feminine distribution. There was a slight diffuse enlargement of her thyroid gland but no tachycardia or other signs of thyroid dysfunction. No abnormal signs were found in the C.N.S., respiratory, alimentary or cardiovascular systems. Her blood pressure was 130/90.

Psoriasis. Gross rupioid lesions covered the scalp with some extension over the hairline. A few fresh guttate lesions were scattered over the limbs, and there was a large healing area over the sacrum. There was widespread light brown pigmentation in recently healed area on the legs, arms and face. Pitting was found on all finger nails, and all toe nails were elevated by subungual hyperkeratosis.

Arthritis. There was considerable limitation of movement with crepitus at both shoulder joints, but only slight aching in the upper arms. Both wrists and several proximal interphalangeal and metacarpophalangeal joints of the right hand were tender and swollen. Most metatarsophalangeal joints of both feet were very tender and there was reduced mobility of several toes. X-ray showed changes which have been described (Fawcitt, J., 1950) as characteristic of psoriasis arthropathica; especially in the feet, where bone destruction with attenuation of metatarsals and joint disorganization were prominent. E.S.R. was 13 mm. in one hour (Westergren) and she had mild normocytic hypochromic anaemia.

On Examination—Mental. Her expression was set and morose; her movements were slow and constrained. She appeared to be slightly anxious, but in general her behaviour indicated apathy. There was scarcely any variation in her mood. Otherwise, she showed no signs of disturbance. Her educational level was low and her intelligence was judged clinically to be low average. At this time she was relatively cheered by the recent physical improvement, but she had good insight for her previous depression. She attributed this to her arthritis and her fear of being crippled. She was less concerned by the psoriasis; when her face was not affected she had become accustomed to this. She ate and slept well and accepted hospital routine without comment.

Psychological tests. Raven's Progressive Matrices I.Q.=92; on the Minnesota Multiphasic Personality Inventory she achieved normal scores on all scales; Wechsler-Bellevue, Full Score I.Q.=89; Verbal I.Q.=77; Performance I.Q.=104 (a result in accord with her record). The clinical impression of emotional inhibition and a sense of insecurity was confirmed by her performance on the Rorschach test, to which she gave very few responses. These were also compatible with some degree of depression. The Make a Picture Story Test result suggested, in addition, that difficulties of sexual adjustment were prominent. This appeared to consist in an ambivalent attitude towards men and towards attaining full feminine maturity.

Clinical Course and Treatment. Throughout her stay in hospital she was seen every day for the purpose of observation. During the first month, while psychological and other tests were done, no special treatment was given. There was little change in her physical signs but symptoms of mild affective disturbance left her and her mood reached a level that was regarded as usual for her. From 25 July, for 6 days, she was given an inert placebo mixture four times a day orally. This was indistinguishable by taste or appearance from the Cortisone mixture given subsequently. While she was receiving placebo, physical signs were unchanged, but for a day or so she was more morose and subdued. At the time she denied feeling different, but later admitted that she had felt "depressed". On 1 August, Cortisone acetate was substituted for the placebo. She was given a total of 4762·5 mg. over 45 days. The initial dose of 100 mg. daily was gradually increased to a maximum of 150 mg. daily which she took for one week. Thereafter it was withdrawn over 17 days, and was followed by a further 15 days of placebo.

After the first few days on Cortisone there was a rapid improvement in joint symptoms. Full mobility at the shoulders was regained, muscle power became normal and she was able to walk on her toes for the first time for 5 years. At the same time psoriatic lesions steadily healed, pigmentation faded and, at the height of her improvement, apart from residual staining, her skin, including the scalp, was normal. A mood change was apparent on the first day of treatment when she spontaneously said she felt better, and was heard whistling and humming as she walked. This was followed by a few days during which she was once more gloomy and listless. In the next week her mood was variable, but by the time she was having 125 mg. daily she was consistently cheerful. By this time she was more animated, talked as much as any patient in the ward and smiled freely at interviews. She was even ashamed of her talkativeness and admitted that she tried to suppress a new tendency to giggle. While on 150 mg. daily there were times when her high spirits were immediately apparent. She giggled, grinned and joked with patients, and had a flippant, jaunty manner. She never referred to her loss of physical symptoms unless asked; then she would admit her pleasure at this. She later claimed that she had never in her life felt as happy as at this time.

When the dose was reduced, and after Cortisone was stopped on 17 September, fresh psoriatic lesions appeared on her scalp and face, and there was a slight relapse of joint pain and swelling. Meanwhile she remained steadily cheerful and contented, but the signs of euphoria had gone. A month later her scalp was as crusted as before and several joints were tender and ached. Her manner and mode of talk was again gloomy and constrained, and at times she was outspoken when annoyed, in a way she had not previously shown in hospital. By November her skin was again as it was on admission, and her joints were worse. Mentally she was little different from how she had been before treatment began.

On 21 November, 1952, inert intramuscular injections were started, preparatory to a course of A.C.T.H. These were given for 10 days. At first she was very upset by the injections; she became manifestly anxious and depressed. When the injections were transferred from the buttock to the arm she was relieved. She said she had always been distressed by injections given "behind her back". Before the placebo course finished her mood had returned to its previous level; there had been no change otherwise. A.C.T.H. was started on 1 December. This was given intramuscularly twice daily over 74 days until 6 February, 1953. She received a total of 5027·5 mg. The initial dose was 60 mg. daily; the maximum dose of 100 mg. daily was started in the 5th week and given for 17 days. A.C.T.H. was withdrawn over 3 weeks and followed by a week of placebo injections.

The physical response to A.C.T.H. was more striking than it had been to Cortisone. Her psoriasis healed more rapidly and ultimately cleared without trace. Her arthritic symptoms were completely relieved, and, apart from mild, transitory symptoms during the withdrawal period, this remission was maintained until several weeks after treatment stopped. By contrast, signs of renewed psoriatic activity appeared as soon as the dose was reduced to 50 mg./day, and this relapse progressed until it was halted by topical therapy two months later.

During the early stages of physical improvement, her mood changed quickly, with a return of the spontaneity, friendliness and the tendency to laugh immoderately that she had shown while on Cortisone. When the dose had been raised to 75 mg./day she displayed a further elevation of mood. She said "I feel happier today than I can remember"; she remarked that she was now continually wanting to laugh. She attributed her good spirits to the loss of joint symptoms. Within two days she had lost her cheerfulness and at no time while on A.C.T.H. did her mood regain a similar high level. After a few days on 100 mg./day, by which time she had lost all physical symptoms, she complained of feeling restless and irritable. A few days later she was obviously depressed. She became solitary and inactive, and was retarded in talk and movement. She described a "fed up feeling . . . it's an awful feeling . . . I keep trying to get out of it, but it just won't move . . . I wasn't like it on the other one (Cortisone)". She was unable to recall her earlier high spirits; she said she thought she had felt more or less like this ever since the present treatment had started. There was little change in this mild depressive state for four days. For two more weeks she remained subdued and gloomy, but by the time A.C.T.H. had been reduced to 25 mg. per day she had regained her good humour, interest and activity. She was unconcerned by the return of her psoriasis: "I feel fine apart from the irritation on my head . . . I feel quite happy." But a few days later she was again mildly depressed, and this variability continued until the placebo injections stopped. Thereafter she reached an equable state of amiable contentment which continued until she left hospital on 14 April, 1953.

During both courses of treatment, there was a moderate degree of facial rounding and generalized skin bronzing; but an appreciable increase of hair growth on face, arms and legs occurred only during A.C.T.H. therapy. These changes receded within a few weeks after the drugs were stopped. Menstruation continued regularly throughout her time in hospital.

Special Investigations. Thyroid function; B.M.R. +2 per cent.; serum cholesterol 175 mg. per cent.; urinary excretion of Radio-active iodine—normal. Glucose Tolerance: a "flat" curve: E.S.R. rose to 15–20 mm. 1st hour (Westergren) before and after treatment; fell to below 10 mm. during each course.

Serum electrolytes: within normal range throughout; on maximum Cortisone dose, Na. = 317, K. – 17·2 mg. per cent.; on max. A.C.T.H. dose Na = 339, K. = 18·5 mg per cent. Blood count: there was a mild normocytic hypochromic anaemia; a moderate rise of total white cells occurred during each course.

Eosinophil count (see Fig. 1): there was a definite but irregular depression of eosinophils from a pre-treatment range of 61–169 per c.mm. to the minimum figures 15 and 10 per c.mm. on Cortisone and A.C.T.H. respectively.

17-Ketosteroids. Estimations of 24-hour urinary excretion of total 17-ketosteroids were done by the standard method recommended by the Medical Research Council (1951). There were high levels before and after treatment. When values during the four weeks immediately after each course are omitted to exclude any "rebound" effect, the non-treatment range was 12·0–40·3 mg., average = 28·9 mg. Values during Cortisone therapy were considerably lower; on maximum dosage the range was 6·4–14·3 mg., average = 10·9 mg. During the A.C.T.H. course high values were maintained and some increase of output occurred; on maximum dosage the range was 20·9–44·4 mg., average = 32·2 mg.

In view of the high 17-ketosteroid output, perirenal air studies were done at the Hammersmith Hospital; radiographs showed normal outlines of suprarenal glands. Skull X-ray showed a normal pituitary fossa. The clitoris, uterus and adnexae were found to be normal; there were no clinical signs of virilism or of abnormal fat distribution. It was concluded in consultation with Dr. Russell Fraser that there was no gross disturbance of her adrenocortical function.

Clinical Rating. For the purpose of easy comparison her clinical course was given a daily rating. Psoriasis was selected for this because it lent itself better to objective estimate than her arthritic symptoms, and because changes in the latter were less pronounced. Her skin condition was rated on a 5-point scale: 1. Normal skin; 2. Residual healing only; 3. Mild chronic and/or early fresh lesions; 4. Moderate activity; 5. Severe activity.

Similarly, a 5-point scale was used for rating Mood, thus: 1. Depressed; 2. Low-spirited; 3. "Normal"; 4. High Spirited; 5. Euphoric or elated. For this purpose euphoria was judged to be present when elevated mood was accompanied by impaired control of emotional expression, such as irrepressible giggling.

These clinical rating and 17-ketosteroid values are shown in Fig. 1 over a 38-week period extending from 2 weeks before Cortisone was started until 2 months after A.C.T.H. was stopped. The eosinophil counts are also shown.

DISCUSSION

It may be seen that there are four general features in the relationship between the clinical course, 17-ketosteroid output and therapy as represented in Fig. 1.

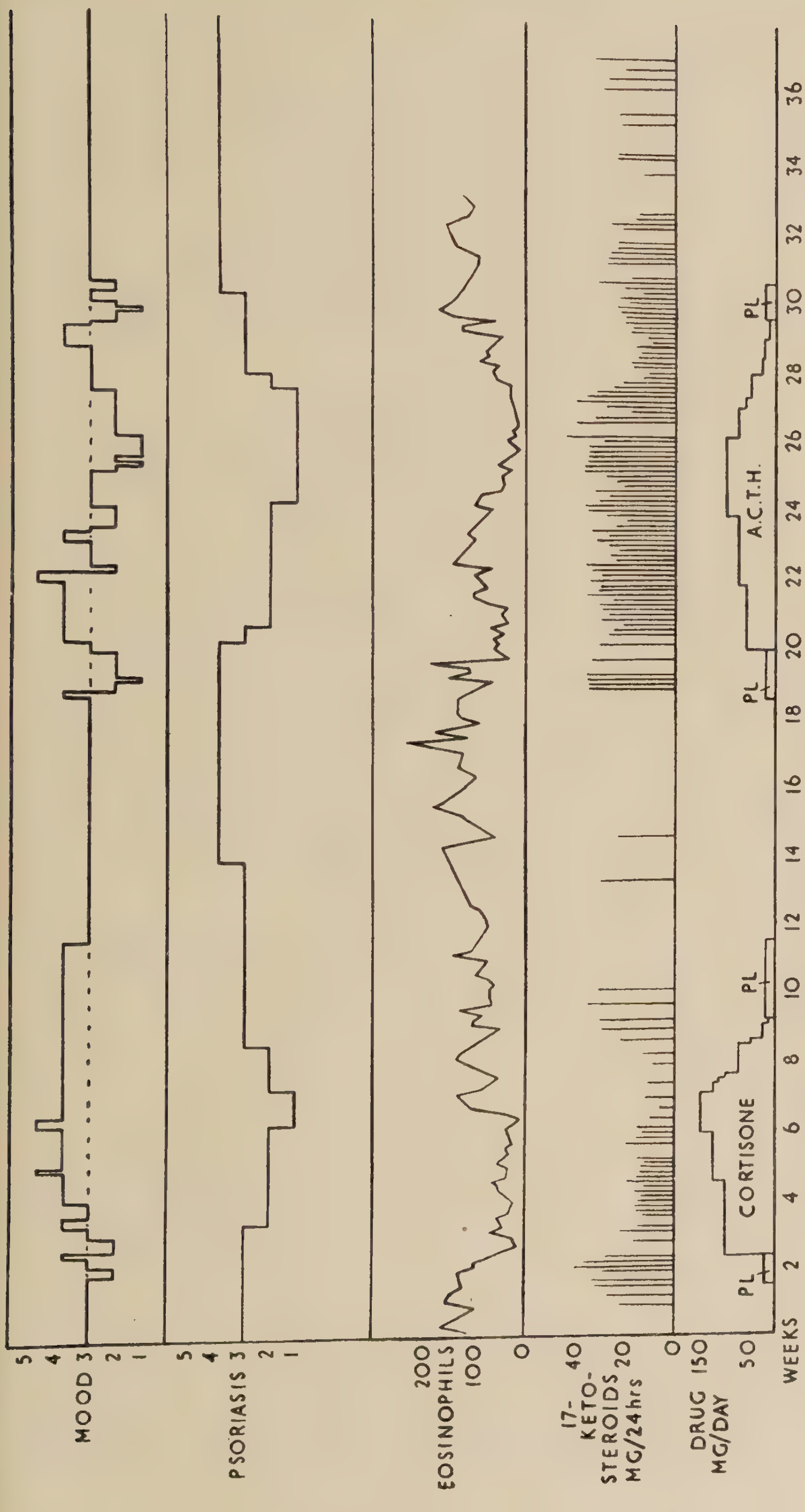

FIG. 1.—Changes in Mood, psoriasis, urinary 17-ketosteroids and direct Eosinophil Count during treatment with Cortisone and A.C.T.H.

PL=placebo.

Mood: 1=Depressed, 2=low-spirited, 3="normal", 4=high spirited, 5=euphoric or elated.

Psoriasis: 1=Normal Skin, 2=Residual healing only, 3=mild chronic and/or early fresh lesions, 4=moderate, 5=severe activity.

1. In each course of treatment, during the early stages of rapid physical (psoriatic) improvement, mood was at or usually above the normal level.

2. When higher, and particularly maximum doses were given, when psoriasis was cleared to an equivalent degree by both drugs, the corresponding mood levels were different. During the Cortisone course there was a sustained elevation, amounting at times to euphoria; during the A.C.T.H. course it remained at or below the normal level, and for some time she was manifestly depressed.

3. These opposing trends of mood are matched by the opposite effects of Cortisone and A.C.T.H. on 17-ketosteroid output. On maximum Cortisone dosage this was reduced to an average of 10·9 mg. in 24 hours, whereas at the corresponding stage of A.C.T.H. therapy the average output was as high as 32·2 mg./24 hours.

4. At times other than when her physical condition was most improved, consistent associations between 17-ketosteroid and mood levels were not apparent. For example, comparison of the findings around the 2nd, 10th, 19th and 37th weeks, shows similarly high 17-ketosteroid values at these times, but considerable differences in the corresponding levels of mood.

It is necessary at this stage to consider certain factors which might have influenced her mood at the time of greatest physical benefit from each drug. Arthritic symptoms: on A.C.T.H. she was entirely free from these; on Cortisone, although shoulder joint mobility was still slightly reduced, the patient was scarcely aware of this. Menstruation occurred at this stage during both courses. She remained on the same ward, and was given the same opportunities for activity and recreation throughout her stay. She suffered no financial loss while in hospital, and a job was kept open for her. Discussion with the patient and her relatives at the time and subsequently yielded no indication of any prominent psychogenetic factors to which the most pronounced and sustained affective changes could be attributed. Finally, there seem to be no grounds for postulating the occurrence of random and paradoxical mood swings, to which the patient was not prone.

It is now possible to interpret the findings in the following way. The patient's mental state, especially her mood, was mainly under the immediate control of three groups of factors; (i) the state of her physical disease, and particularly the rapid changes produced in this by therapy; (ii) endocrine functions reflected by 17-ketosteroid excretion; and (iii) environmental and psychological events such as those which have just been considered. The continuous interplay of all these variables would obscure the relationship between mood and any one factor. Also, any overwhelming contribution from one type of influence would alone create its characteristic effect on her mood. For example, her spell of depression in the 19th week when placebo injections were started was clearly related to her dislike of intramuscular injections: similarly the rapid improvement in physical symptoms in the early stages of both Cortisone and A.C.T.H. courses was associated with elevated mood. It remains, then, to observe the effect of bringing certain of these factors "under control". For this purpose, suitable conditions obtained when she was receiving high doses of both drugs. At these times, as far as it is possible to judge in an ordinary clinical setting, environmental and other contingent factors were equivalent. In each instance her physical disease was under fullest control and she was free from symptoms. It is, therefore justifiable to examine the relationship at these times between mood and the remaining variable; that is, 17-ketosteroid values.

Under these circumstances, the associations of reduced 17-ketosteroids with elevated mood, and of raised 17-ketosteroids with depressed mood assume significance.

It is interesting to note that the mood changes in this patient were relatively mild. They were, in fact, of a degree and quality which could easily have encouraged the view that they were due to other factors: one might have postulated either pleasure at symptom-relief, or, by contrast, an unacknowledged reluctance to lose the benefits of illness. Yet there can be little doubt that the 17-ketosteroid changes, which related to her mood variation, were produced by the action of the drugs on her adrenal cortex. The suppressive action of Cortisone was probably due to its inhibitory effect on pituitary–A.C.T.H. release (Sayers, G. and Sayers, M. A., 1948; Lewis *et al.*, 1950); although the possibility of a direct action on the adrenal cortex does not seem to have been ruled out. It follows, therefore, that mood changes occurred which were directly attributable to exogenous Cortisone and A.C.T.H.; and, in this patient, the effects of these drugs in this respect were different.

How may these findings be explained and at the same time reconciled with the lack of consistent psychological response to these drugs which is so evident from previous reports? It could be, simply, that this patient's mood was influenced by the absolute levels of circulating androgens, from which the greater part of urinary 17-ketosteroids is thought to derive; so that Cortisone elevated her mood by reducing androgen secretion, whereas A.C.T.H. produced the reverse effect by accentuating one of the endocrine components of her depressive disposition. It might be argued, also, that a similar relationship between mood and 17-ketosteroids has not been found generally in patients under treatment, because most of these begin with low rather than high 17-ketosteroids; hence this patient was unusual in a significant respect. This explanation, however, throws no light on the general problem; furthermore it takes no account of the increase of Cortisone or Cortisone-like activity which must have occurred during both courses of treatment. In the first this was due to oral dosage with Cortisone, in the second it was provoked by A.C.T.H. When this factor is considered, it suggests that mood may have been influenced, not by absolute levels of individual adrenocortical products, but by changes in the relative proportions of circulating androgens and Cortisone or its equivalent. The exact ratio of these is not known in this case, because only 17-ketosteroids were estimated, but there is some warrant for the view that a disproportion of this kind may be associated with mental changes.

Hoagland and his colleagues (1953) found that "schizophrenic patients showed lower than normal rates of excretion of corticoids and phosphates, and thus displayed at rest evidence of both hyperadrenalism and hypoadrenalism". Rowntree and Kay (1952), who made detailed observations of two patients with recurrent schizophrenic episodes, found evidence of "a dissociation between different adrenocortical steroids, the various stages of an attack being associated with a relative preponderance of different steroid fractions". At the height of an attack there was a preponderance of androgenic substances. Reiss and his colleagues (1949) report a case which is of particular interest in this connection. Their patient had alternating phases of mania and depression. They found an inverse relationship between beta-ketosteroid and low cortin excretion; during the transition to mania beta-ketosteroids fell and cortin excretion rose. It is possible that a similar disproportion, or even an inverse relationship of this kind accompanied the mood changes of the patient reported here. It is evident that "the point at issue is not entirely whether the adrenal gland is hyperfunctioning or hypofunctioning. Qualitative rather than quantitative changes in adrenocortical output may be the key to understanding the relationship between the endocrine system and mental illness" (Cohn *et al.*, 1954).

Regarded in this light it is not surprising that characteristic differences between the psychological effects of giving Cortisone and A.C.T.H. have not been demonstrated. If these effects depend on a disproportion such as between androgens and corticosteroids, either drug may produce them. Whether there is a specific association between the type of disproportion and the quality or incidence of mental changes can only be discovered by serial observations in many cases. In any event it is probable that these reactions are at least partly determined by the functional state of the adrenals before the drugs are given.

The search for significant correlates of the mental symptoms occasioned by A.C.T.H. and Cortisone therapy has not, so far, been fruitful. Individual susceptibility to them does not appear to be related to either the response to previous courses of treatment (Clark *et al.*, 1953) or previous mental disorder or emotional instability (Lewis and Fleminger, 1954). It is doubtful whether the psychological mechanisms which have been postulated in some instances are more generally applicable than the electrolytic disturbances that have been reported (Ransohoff, W., 1951). It is likely that a complex of factors is concerned. Among these, the modification of adrenocortical function induced by these drugs is probably always contributory, and, given suitable conditions, may sometimes be crucial.

SUMMARY

An account is given of the response to treatment with Cortisone and A.C.T.H. of a young woman with psoriasis arthropathica.

The relationship between changes in her mood, physical symptoms and urinary 17-ketosteroid values, indicates that mood variations occurred, which were directly attributable to the drugs, rather than to symptom-relief or other factors.

Cortisone led to an elevation of mood; A.C.T.H. provoked depressive symptoms.

It is suggested that Cortisone and A.C.T.H. may have influenced mood by producing changes in the relative proportions of androgens and other adrenocortical products.

ACKNOWLEDGMENTS

I wish to thank Professor Aubrey Lewis, under whose direction the treatment and investigations were done, for his advice and encouragement. I am indebted to Dr. J. H. Rey, Senior Lecturer, Institute of Psychiatry, for his helpful criticism, and to Dr. D. R. C. Willcox, Clinical Pathologist, Bethlem Royal and Maudsley Hospitals, who supervised the laboratory studies.

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THE RESULTS OF THE EXPERIMENTAL ADMINISTRATION OF AMPHETAMINE SULPHATE IN OLIGOPHRENIA

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A NUMBER of drugs have been employed in an attempt to increase the mental capacity of oligophrenics. The effect of thiamine on learning demonstrated by Harrell (1943, 1946) led Rudolf (1949, 1950) to use this vitamin in the treatment of oligophrenia. Similarly, the early studies of Zimmermann and Ross (1944) on glutamic acid resulted in a large number of papers on its debatable effect in feeblemindedness (Zimmermann, Burgomeister and Putnam, 1946, 1947, 1948; McCulloch, 1950; Ellson, Fuller and Urmston, 1950; Quinn and Durling, 1950; Lafon, Faure and Bascou, 1952; Oldfelt, 1952). The results of celastrus paniculata on mental defectives have been described by us elsewhere (Morris, MacGillivray and Mathieson, 1953, 1954).

Amphetamine ("benzedrine", β-phenylisopropylamine) is a sympathomimetic amine resembling ephedrine and adrenaline, but differing chiefly in its greater abilities to stimulate the higher centres of the nervous system and particularly the cerebral cortex. This mechanism of cerebral stimulation has not been fully elucidated. Blaschko (1940) suggested that the ability of the sympathomimetic amines to act as analeptics can be directly correlated with this ability to inhibit amine oxidase in vitro. Mann and Quastel (1940) found the respiration of brain tissue to be inhibited by certain amines such as tyramine and isoamyline which are oxidized to ammonia and their corresponding aldehydes by amine oxidase. The addition of benzedrine increases oxygen consumption by the brain by binding amine oxidase so that toxic aldehydes cannot be liberated. However, amphetamine cannot increase the respiration of brain inhibited by anaesthetics or produce an increased oxygen consumption by normal brain tissue. It is doubtful whether the peripheral effects of amphetamine on adrenergic structures can be linked with the excitatory effects on the central nervous system.

The effects of amphetamine on the central nervous system have been summarized by Wilson and Schild (1952) as follows. The diffident individual becomes more confident, with greater capacity to make decisions and his thought processes are speeded up. This is often shown in an increased facility by the patient to express himself in speech. Although the capacity to do simple additions is increased, there is less effect on the ability to concentrate, and some subjects find themselves slower in solving more complicated problems which demand concentration. Amphetamine does not increase the efficiency of work; Browne (1947) observed that if the drug was given to fatigued pilots it made them feel better, but their performance did not improve and if the job was difficult their performance in fact deteriorated.

The euphoric action of amphetamine was first recorded by Peoples and Guttmann (1936) while experimenting on its action in raising the blood pressure. Subsequently Guttmann and Sargant (1937) reported their work on 250 patients and controls at the Maudsley Hospital. They found an increased confidence, increased initiative and increased ease of making decisions, while the patients became more talkative. Some subjects became restless, and vasolabile persons tended to complain of dizziness, shivering, palpitations, tremor or anorexia. There is considerable individual variation in the response to these sympathomimetic amines. Further early descriptions of the psychic results of amphetamine are those of Myerson (1936), Davidoff and Reifenstein (1937), Nathanson (1937), Fisher (1937), Bahnsen, Jacobsen and Thesleff (1938) and Jacobsen (1939).

Increased mental performance by actual objective measurements has also been described by some workers. This was first suggested by Sargant and Blackburn (1936) who investigated the results of amphetamine on 48 adult mental hospital patients, using Cattell's intelligence tests, and reported an 8 per cent. improvement in test scores. The results reported in this paper were not statistically significant and can be largely discounted for this reason. Subsequently, Molitch and Eccles (1937) studied the effect of amphetamine on children's intelligence scores. Ninety-three boys between the ages of eleven and seventeen of varying mental levels were tested at intervals before and after a placebo or amphetamine was ingested. It was noted that both groups improved their scores, but the children tested after amphetamine exhibited a greater improvement than those taking the placebo. The tests used were the measuring of hand grip by the Smedley dynamometer, the Witmer formboard, a memory-for-design test and three standardized verbal intelligence tests, i.e. the Kent E.G.Y., the Morgan intelligence test and the Kuhlman-Anderson intelligence test. The Kleemeiers (1947), in an interesting experiment, took as their subjects twenty-seven intelligent university students. These were given glucose and amphetamine alternately and it was found that all speed tests showed an increase in "t" score, that is, the ratio of the difference between means to its standard error. The testees showed increased performance with amphetamine on a number of timed tests and this they believed to be due to an increased flexibility. There was no differential effect on fast and slow workers. Performance was apparently readily facilitated on the multiplication, selective substitution and arithmetic speed tests used in this study. Facilitation was also noted on the letter series, paper and pencil, motor over and under, and word completion tests, but these cannot be accepted as being highly reliable.

Hill (1947) points out that the improved performance which has been reported on intelligence scores under the influence of amphetamine is due to increased motor and speech activity, i.e. a change in the executive rather than in the affective elements of the mind. This, he states, occurs in normal people, mental patients and in children. Rudolf (1947) believes that relief of fatigue may account for the increase in the scores, and emphasizes that this is particularly likely in those patients reported by Sargant and Blackburn (1936), as these were psychopaths who are known to be especially liable to fatigue.

The use of amphetamine in the treatment of behaviour problems in children has been discussed by Lindsley and Henry (1942). They noted a great improvement in behaviour in such cases but the electroencephalograms were unaltered. The explanation of this according to Walter (1950) is that in these children certain cerebral functions have developed unusually slowly and the child is faced with an environment which he is not yet able to tolerate and manipulate in a reasonable way. Most of these children are not able to exploit any particular ability, and resort to sulkiness, defiance of authority or violence in an attempt to alter their surroundings. For such children amphetamine provides a substitute for the natural brilliance of the better endowed child by enhancing their interest and perhaps their ability. The drug cannot instantly accelerate the development of the cortico-basal mechanisms, so that the theta activity in the EEG persists, but it does seem able to stimulate those activities which are already mature.

The results of amphetamine sulphate on the EEG in the normal person are unspectacular, as might be expected. Corresponding presumably to the increased alertness and psychic activity is a modification of the cortical frequencies similar to that accompanying the change from rest to attention. This was shown with the aid of the Grass frequency analyser by Gibbs and Maltby (1943) who gave 20 milligrams of the drug intravenously. 10 milligrams of the sulphate produce no detectable change in the unanalysed EEG (Gibbs, Gibbs and Lennox, 1937; Blake, Gerard and Kleitman, 1939). Sleep tends to be lighter after amphetamine sulphate, and the delta activity is reduced in voltage and amount (Blake *et al.*, 1939). Although amphetamine is a powerful vasoconstrictor it apparently does not reduce the cerebral blood flow (Schmidt, 1944).

The effects of amphetamine on mentally deficient children have received little attention. The work of Bradley (1937) who found that administration of the drug tended to improve school performance, particularly arithmetic, in one half of the children treated, led Cutler, Little and Strauss (1940) to investigate the results of the drug on oligophrenics. They approached the question from two angles; the first problem being to assess the effect of a small daily dose of amphetamine over a protracted period on the capacities of mentally defective children, which might be measured by psychometric tests; the second to determine whether gain would appear in psychologically measurable skills when a relatively high dosage of amphetamine was administered only once to children of like intelligence. They concluded that medication in small doses did not show much if any significant effect on the mental reaction of defective children as measured by the Stanford and Terman Merrill Form M Revision of the Binet, the Grace Arthur Point Performance Scale, the New Stanford Achievement Test, the Vineland Social Maturity Scale and by tapping and cancellation tests. The stimulation given by amphetamine did not measurably improve test achievement immediately after administration or subsequent to a period of six months after medication had been withdrawn. There were no changes in behaviour, either favourable or unfavourable, to be observed in the group which received amphetamine in small doses as compared with the matched group of controls. It was noted that amphetamine given as a sudden stimulant affected favourably the outcome of the following tests—Tapping, Porteous Mazes, Knox Cubes, Seguin and Ferguson Form Boards and Healy II Picture Completion. It was concluded that these results were explained by amphetamine stimulating particularly psychomotor activity which is involved to a greater extent in these performance tests. They observed further, that amphetamine tended to affect the utilization of learned material in academic fields as shown in the New Stanford Achievement Test. A similar improvement in normal boys on the Stanford Achievement Test was reported by Molitch and Sullivan (1937). Moskowitz (1941), in an essentially clinical study, points out that in selected cases of uncomplicated oligophrenia, prolonged administration of amphetamine sulphate raises the ability of the central nervous system of the mentally handicapped to the point where educational training can be utilized, resulting in a greater performance ability. He suggests that the selection of these cases can be correlated with somatic factors, body measurements and response to adrenaline injection.

In view of the comparative paucity of the literature concerning the action of the drug on mental defectives it was decided to set up a carefully controlled investigation on the clinical action and psychological effects of the drug on a group of institutionalized oligophrenics.

Selection of Groups to be Tested

Patients in the hospital group were surveyed and a total of fifty were selected with an age range of 15½ to 32 years and intelligence quotients from 60 to 74. Epileptics and post-encephalitics were excluded as also were those with known psychopathic tendencies or subject to emotional or other stress from friends or relatives. Some subjects who had been used in previous experiments in relation to celastrus paniculata were included, but only in the control group. Two groups were then formed, matched for age and intelligence quotient, the experimental group of eleven males and fourteen females with an average intelligence quotient of 66 on the Terman Merrill scale and an average age of 22·5/12 years, and the control group of twelve males and thirteen females who had an average intelligence quotient of 66 on the same scale and an average age of 22·5/12 years.

The following test battery was employed in the experiment:

Terman Merrill Revision of the Binet Scale, Form L or M, before and after administration.

Cattell's Non-Verbal Intelligence Scale I, Form A before and Form B after administration.

Kohs' Block Designs before and after administration.

Tests of Learning

(1) Verbal Paired Associates. The test consisted of a list of numbers associated with animals, the names of the animals corresponding to the numbers being recalled after one trial.

(2) Non-Verbal Paired Associates. Coloured cards were matched with designated shapes of openings in a box. This, like the preceding test, was scored for time and for the number of prompts required before two correct performances.

(3) Number Sorting. Numbered cards were placed in irregularly distributed matching compartments in a box, the results being scored for speed and accuracy.

Tests of Voluntary Attention

(1) Number Cancellation. A sheet of numbers in irregular order from 0–9 was given to the candidate who struck out a stated number. The score was based on the number of cancellations made in 90 seconds.

(2) Linking Circles, as in the Kleemeiers' experiment (1947), where testees linked circles set out in irregular horizontal pattern interspersed with X's, before administration; on retest the figures 1 and 2 were substituted respectively. Scores were calculated on speed and accuracy over a period of 90 seconds.

(3) An L's test similar to the G.A.T.B. Test, where the letter was marked by the examinee. Results were scored for speed and accuracy.

(4) The number of X's made in a minute.

(5) Arithmetic. Ungraded sums in addition were scored for the number completed and the number of errors.

(6) Fluency. Verbal enumeration and scoring of "the number of things that can be bought" and on retest "the number of things that one can see" in a minute.

Memory

(1) Visual apprehension was tested by five-second exposures of three sets of groups of ten common objects. Points were given for accuracy. Inaccuracies were measured by the number of articles falsely recalled.

(2) Memory for Design. Geometrical shapes were reproduced from memory from two cards of nine drawings, each exposed for fifteen seconds. Scoring was computed on correct placing and accuracy.

Level of Aspiration Test

The number of taps per minute made by the examinee with a Morse key were measured by an impulse counter. The three ratings were: the number of taps; judgment discrepancy score based on the difference between actual performance score and judgment score on trial X, underestimation of past performance giving a negative score, overestimation a positive one; goal discrepancy score based on the difference between actual performance on trial X and aspiration for trial X+1.

The same examiner gave the group tests before and after administration, the same procedure being followed in the case of the individual tests. Closely parallel tests were substituted after administration.

Administration

By courtesy of the makers a supply of identical dummy tablets containing an inert substance (lactose) was provided and the daily dosage of amphetamine and the placebo was arranged as follows—5 mg. for the first week, 10 mg. for the second week, 15 mg. for the third and fourth weeks, the latter dosage being continued until testing was completed.

During this period the experimental and control groups were weighed weekly, their sleep records surveyed and their behaviour observed by skilled nursing staff for any variation in either behaviour or working capacity. The side effects of the drug were the subject of enquiry and the evidence of any was reported. The nursing staff concerned were unaware which tablets consisted of placebo.

Intelligence Test Results

After administration both groups showed similar slight improvements in their scores on the three intelligence tests. The changes were exceedingly small on the Cattell Scale being less than one point of average I.Q. in either group, a consistency which contrasts strikingly with results reported on this test in a previous experiment (Sargant and Blackburn, 1936). The preliminary and post-treatment ratings on Kohs' Block Design test showed the high positive correlation of ·95 in the control group and ·93 in the experimental group. On the Terman Merrill Scale there was an average improvement of four I.Q. points in either group, this may be partly due to familiarity with the test which is in current use in this hospital group, but the change is insignificant and comparable with those reported in previous experiments, e.g. (Cutler *et al.*, 1940). The mean intercorrelation of the three preliminary test scores of the whole group was relatively low, being +·47.

The results indicate no improvement in intelligence due to administration and in fact the control group average improvement on each test was slightly greater than that of the experimental group.

Tests of Learning

On the verbal paired associates retest both groups shortened their learning time and reduced the number of prompts required after administration, the control group improving slightly more than the experimental group. Scores were satisfactorily distributed, the difference between the groups was insignificant and practice effect was slight.

On the non-verbal paired associates test there was a statistically significant reduction in the number of prompts needed by the control group in the retest, as compared with the experimental group. This is largely due to the major improvements in the scores of four patients. It indicates the risk of obtaining superficially misleading results even in carefully controlled experiments. The control group also learned more quickly on the retest than the experimental group but the difference in this case was not significant.

Both groups took approximately twice as long to establish seven verbal associations as they did eight visual associations. In view of the testee's limited range of intelligence there were wide variations in the learning times of both groups. On the verbal test initial learning times ranged from 27 seconds to 34 minutes 47 seconds and on the non-verbal test from 25 seconds to 16 minutes 7 seconds.

In the number sorting test both groups showed practice effect, being initially quicker, but after administration they reduced their time proportionately less over five trials. This was due to their improvements bringing them nearer to the minimum time required to place the cards in the compartments.

Tests of Sustained Voluntary Attention

The majority of patients in both groups showed slight improvements after administration, attributable to practice effect.

In the number cancellation test the gains were similar in the two groups, but in linking circles, statistical analysis revealed that the improvements in the scores of the experimental group were significantly greater than those of the control group, these gains were also satisfactorily distributed. The experimental group made more errors on the retest than did the control group, but this difference was not significant. The retest results of both groups on the L's test and on the X's in a minute test also showed similar minor increases.

The Arithmetic test results of the two groups were essentially the same before and after administration but the experimental group increased their errors slightly more than the control group. This stability in the level of performance is also in contrast to gains reported in previous experiments. There was no significant change in verbal fluency in either group.

Tests of Memory and Apprehension

The average span of visual apprehension of common objects was almost identical in the two groups, namely five out of ten objects in fifteen seconds exposure, and remained essentially unchanged after administration. Both groups reduced the number of false recollections on the retest, the experimental group making a greater reduction than the control group contrary to what might have been expected.

In the recall of designs from memory the control group average score increased very slightly more than that of the experimental group but the experimental group attempted rather more drawings than the controls after administration. The difference was not statistically significant. Both groups recalled approximately half the nine designs on each card, scored for placing and accuracy.

Level of Aspiration Test

There was little change in the number of taps made after administration and the averages of the two groups were closely similar.

In predicting their future score the experimental group was slightly more ambitious than the control group. At the first testing both groups showed some optimism. After administration the average goal discrepancy of both groups was less, being nearer their last actual score. This conservative tendency was slightly greater in the case of the experimental group, a fact which seems to contraindicate euphoria. Both groups tended to under-estimate their past performance on the first testing and a similar trend was evident after administration although it was less marked in both groups.

The general aspect of the test results indicates little difference between the number of improvements in the scores of the two groups, such as were found, being within the limits of chance variation. On a total of 650 ratings, the experimental group showed 361 improvements against 348 in the control group. It is of interest that these improvements were normally distributed among the members of both groups, the average number in the experimental group being 14·4 with a range of 8 to 21 against an average of 14·0 with a range of 8 to 19 in the controls out of a total of 26 ratings. The improvements found were insignificantly small and only three of the experimental group and two of the control group showed more than four marked improvements on individual tests.

The "t" scores showed a significant difference between the improvements of the groups in only two instances. The experimental group improved more than the control group in linking circles and the control group required significantly fewer prompts in the re-test of the Non-Verbal Paired Associates. The control group showed a very slightly greater but not significant improvement compared with the experimental group in seventeen of the remaining twenty-four ratings.

Physical and Mental Condition

All patients were weighed weekly during the experiment and at the conclusion of treatment the experimental group had lost an average of two pounds in weight while the control group were unchanged on average. In the experimental group nausea was noted in one male and two female patients, while a hypomanic state with restlessness and aggression was reported in three cases, who comprised the most psychologically immature and emotionally labile members of the group. No other toxic effects were observed. Three other cases were improved in working capacity and interpersonal relationships. In the control group no behaviour changes were noted beyond a phase of aggression in one patient for a brief period due, we understand, to a family quarrel.

	Scores						"t" Score
	Experimental Group			Control Group			
	Before	After	Improvement	Before	After	Improvement	
Terman Merrill. I.Q.	65·5	69·4	3·9	66·3	70·7	4·4	−·57
Cattell. I.Q.	61·0	61·3	0·3	64·7	65·3	0·6	−·18
Kohs' Blocks. Mental age in years	9·11/12	10·4/12	5/12	10·5/12	11·8/12	1·3/12	−·51
Verbal Paired Associates:							
A. Time	7′ 29″	7′ 17″	+12″	6′ 56″	5′ 49″	1′ 7″	−·40
B. Number of prompts	18·4	18·4	0	20·4	16·5	3·9	−·91
Non-Verbal Paired Associates							
A. Time	3′ 4″	3′ 52″	−48″	4′ 34″	2′ 53″	+1′ 41″	−1·72
B. Number of prompts	17·0	19·4	−2·4	31·3	17·5	13·8	−2·16
Number Sorting:							
Times for first trial (in seconds)	35·4	26·9	8·5	33·7	25·0	8·7	−·05
Percentage of improvement on fifth trial	33·1	26·4	−6·8	37·7	26·4	−11·3	+·64
Number Cancellation	36·5	46·3	9·8	39·3	49·1	9·8	−·01
Linking Circles	33·6	43·3	9·7	44·3	46·6	2·3	+2·38
L's test	48·8	56·2	7·4	49·4	57·6	8·2	−·02
X's in one minute	81·6	86·7	5·1	84·0	87·9	3·9	+·28
Arithmetic	36·0	36·6	0·6	35·8	37·7	1·9	−·73
Fluency	19·1	19·1	0	23·8	24·1	0·3	−·33
Visual Apprehension	15·8	16·4	0·6	15·8	17·2	1·4	−1·06
Memory for design	18·4	19·0	0·6	20·2	20·9	0·7	−·06
Level of Aspiration:							
Number of taps	76·2	81·0	4·8	73·2	78·0	4·8	+·02
Goal discrepancy	+2·5	+0·6	−1·9	+1·5	+0·1	−1·4	−·15
Judgment discrepancy	−6·8	−4·2	+2·6	−5·5	−2·3	+3·2	−·31

DISCUSSION

In our experiment no improvement was found in testing intelligence on the Terman Merrill Scale just as Cutler *et al.* (1940) reported only a few small insignificant improvements on the same scale. On the other hand these authors found improvement in the performance tests, due, they suggest, to increased psychomotor activity with sudden administration of the drug. This result is at variance with our experience with prolonged administration where no increased psychomotor activity was noted for example in the Kohs' Block Design Test. Similarly, the scores on the tapping part of our level of aspiration test did not show the improvement reported by these authors. In fairness, it should be stated that their results were based on sudden medication and where prolonged administration was tried, their results were similar to ours. The same applies to number cancellation tests. Apparently the results of these observers were not subjected to statistical analysis.

The results obtained in this experiment compare unfavourably with the claims made by Moskowitz (1941) but he employed a larger dosage coupled with thyroid medication in an essentially clinical study.

Sargant and Blackburn's (1936) findings were based on a study of a group of adult patients in a mental hospital and have already been subject to criticism by Rudolf (1947) who emphasized that the relief of fatigue resulted in increased test scores and postulated that psychopaths show undue proneness to fatigue. In our experiment no change was found on Cattell's Scale; it may be because our testees were functioning at a lower level of mental capacity.

In the linking circles test there was a barely significant increase in the score of the experimental group. This apparent increase was not to be found in other tests involving essentially the same abilities. In our mental defective group we were unable to confirm the claims made by many authors that improvement in arithmetical ability resulted from administration of the drug. Both speed and accuracy were measured and showed no change.

Other investigators who have reported euphoria in normal adults, children and mental hospital patients, have generally based their findings on subjective reports from the patients themselves. It must be generally agreed that the drug does produce euphoria in non-defective patients. Neither Cutler *et al.* (1940) nor Moskowitz (1941) mention euphoria in their experiments, an experience which is paralleled in this study where neither clinically nor in the test used for the level of aspiration was there any evidence of this symptom.

Two previous experiments conducted on patients of this hospital group have resulted in a considerable degree of sophistication in relation to the results of the administration of various drugs. Therefore it is submitted that the traditional suggestibility of the mental defective was probably not a potent factor contributing to the results.

CONCLUSIONS

It is apparent that treatment with amphetamine does not increase intelligence, learning capacity, speed and accuracy of voluntary attention, fluency or memory in mental defectives.

The results of this study do not support the contention that the administration of amphetamine can raise the ability of the central nervous system of the mentally handicapped to the point where educational training can be utilized.

It is of considerable interest that this defective group did not experience the customary euphoria which the drug is so well known to produce.

ACKNOWLEDGMENTS

We wish to thank Dr. M. L. Graeme for his courtesy and assistance, Messrs. Menley & James Ltd., for supplies of the drug and the placebo, and Miss J. M. R. Caseby, M.A., for assistance in the psychometric investigation.

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TYPES OF SYNAESTHESIA

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INTRODUCTION

SYNAESTHESIA is defined by Vernon (1937) as a phenomenon in which "a stimulus presented in one mode seems to call up imagery of another mode as readily as that of its own". The discovery of synaesthesia has sometimes been wrongly attributed to Galton. Galton (1883) certainly describes instances, but reports on earlier descriptions, for example those published in 1881 by Bleuler and Lehmann.

Synaesthesia can be experimentally produced and may continue for a time in individuals not ordinarily synaesthetic. There is much contemporary research interest in abnormal mental states induced by administration of mescaline and chemically related substances (e.g. Hoffer, Osmond and Smythies, 1954). Since synaesthesia is a very frequent symptom of mescaline intoxication, a re-examination of the concept seems opportune. A further reason for this examination is the possibility that such experimentation may produce synaesthesias of types which seldom or never occur naturally. We shall examine instances of both these kinds, and suggest a simple convention which would facilitate more rigorous description and discussion of the various types of synaesthesia.

DEFINITION AND SUGGESTED CONVENTION

The two components of synaesthesia are imagery and sensation, belonging to different sense modes (*vide* Vernon, above). A simple definition might be: "Imagery of one sense mode aroused by sensations of a different sense mode." Two hyphenated words would, then, be sufficient to indicate the different types: "visual-auditory", "auditory-tactile", "visual-olfactory", etc. It would help description if the first word could always denote the *imagery* experience, and the second word always denote the *sensory* experience. Thus the commonest type, visual imagery accompanying auditory sensation, would be termed "visual-auditory synaesthesia". An instance of this kind of synaesthesia is reported by a colleague: "I tend to have visual images of patterns and shapes when I hear music, particularly that of Bach." The example taken illustrates a common kind of visual-auditory synaesthesia. Visual-auditory synaesthesia may assume the form of a "chromaesthesia": when perception of sounds gives rise to imagery of colour. Thus one of our subjects imaged the auditory stimulus of a trumpet as "a bright yellow", and that of a tuba as "a lovely, dark rich, deep red".

On the basis of the convention suggested, it becomes easier to distinguish the principal types of synaesthesia which are theoretically possible: "visual-tactile", "auditory-visual", "visual-kinaesthetic", etc. This raises the question of which of these possible types occur in fact, either naturally or under appropriate experimental conditions. Synaesthesias of any kind are by no means common, and those ordinarily reported tend strongly to be of the visual-auditory type. As illustration of this predominance we may instance Riggs and Karwoski (1934) who, in "summarizing the literature of synaesthesia in children", deal exclusively with cases of visual-auditory synaesthesia. Data obtained by us in another investigation accord with this tendency: synaesthesias, all of the visual-auditory type, were reported by 15 of a group of 110 students. The colour or other imagery tended to occur on hearing music (McKellar and Simpson, 1954).

Synaesthetic Descriptions

From synaesthesia proper, as defined above, we should like to distinguish what might be called "synaesthetic descriptions". Such descriptions comprise the communication of experiences of one sense mode in language appropriate to other sense modes. As Kerr and Pear (1932) remark, "the use of simile and metaphor may perhaps be regarded as the entrance door to synaesthesia". Synaesthetic description embraces one kind of metaphor, which it seems better to distinguish from synaesthesia proper. Such descriptions are often resorted to in the field of taste: for example, we find instances of wines described as, "smooth with no edges on it", "robust and big", and as "having a dry flinty flavour". A colour may be described as "warm" or "cold". More prosaic examples are descriptions of noises as "penetrating" or "jarring".

Synaesthetic descriptions of the visual-algesic kind occur quite frequently, since pain sensations of different kinds are neither conceptualized easily nor communicated readily in literal terms. One colleague frequently thinks of pain in terms of colour: "a green pain—mild pain of the tickling kind; a red pain—sharp and acute; a deep blue pain—throbbing, persistent pain". Toothache he had recently experienced was described in this neologistic way as "a red pain". Another colleague in conversation spoke of the "blue" and "green" pain which she had experienced while at her dentist. When asked by one of the writers what she meant by "blue" and "green" she replied: "It was a sharp, shrill, thin acid green, and an icy blue"! This was a genuine attempt to communicate her way of thinking about pain by a subject who is a poor visual imager. Such synaesthetic descriptions may, or may not, be accompanied by actual synaesthetic imagery. Unless there is definite evidence for such imagery occurring at the time, we should prefer not to classify these descriptions as genuine synaesthesia. For example, although synaesthetic idiom is a habitual component of the last subject's thinking about pain, true synaesthesia is absent. Synaesthetic descriptions appear to resemble synaesthesias in being highly individual and personal. Myers (1911) observes that two synaesthetic subjects may "hotly dispute" over the differences of their synaesthetic imagery (p. 238). Similarly, with the two subjects mentioned who used synaesthetic descriptions of their pain experiences, there was no evidence of agreement. Such descriptions, until "translated" by the subjects, have some resemblances to the neologisms of psychosis.

Some Types of Naturally-occurring Synaesthesia

Occasional accounts of types of synaesthesia other than visual-auditory appear in the literature. Myers (1911) reported that the case of visual-auditory synaesthesia studied by him was also subject to the type we should call "visual-gustatory". This comprised "colour experiences with tastes; these appear generally to be suggested by the colour of the tasting object" (p. 238). Investigations of blind subjects by Wheeler and Cutsforth (1922) yielded descriptions of visual-tactile synaesthesias. One individual, given an object which he had to recognize by touch, reported: "I became aware of two more blunt points . . . There at once appeared visual imagery of a jewelled pin." The subject added that the imagery "was localized at my finger tip" (p. 363).

Even these examples of "other" types of synaesthesia all involve a *visual* imagery component. Naturally occurring cases of non-visual synaesthesias seem to be rarer. Subsequent to our investigation cited above, however, we have observed three such instances: namely, synaesthesias of the kinaesthetic-olfactory, the tactile-visual and the tactile-auditory types. The first occurred in the presence of one of the writers during a class experiment in which olfactory stimuli were being assessed against Crocker's Odour Standards (1946). The subject was given, as olfactory stimulus, a bottle containing cod-liver oil. He was unable to identify it immediately, and in the course of his efforts remarked, "This gives me a funny feeling of being on a ship". (Question by L.S.): "Was it a visual image?" The reply was: "No, a definite feeling of standing on a deck rolling from side to side—a kinaesthetic experience." We should accept this as a genuine instance of a kinaesthetic-olfactory synaesthesia; conditions were such as to exclude any likelihood of gross deception and the subject was unaware of any particular interest in synaesthesia phenomena on the part of the experimenter. The tactile-visual and the tactile-auditory synaesthesias were described by S.F. (later one of the subjects of the mescaline experiments) as

	SENSORY EXPERIENCE							
IMAGERY EXPERIENCE	VISUAL	AUDITORY	TACTILE	GUSTATORY	OLFACTORY	KINAESTHETIC	THERMAL	ALGESIC
VISUAL	–	NE	NE	N	E	E	E	E
AUDITORY		–						
TACTILE	NE	NE	–		E			
GUSTATORY				–				
OLFACTORY					–			
KINAESTHETIC					N	–		
THERMAL	E						–	
ALGESIC		E						–

FIG. 1.—*Types of Synaesthesia:* Those types of which instances are reported in the present paper have been marked ; "N" indicates a naturally occurring, and "E" an experimentally produced, instance of synaesthesia.

forming part of her natural synaesthetic experiences. Her strongest imagery is tactile, and she normally tends to describe the feel, rather than the appearance, of things. Thus, one person was described as "looking like a baby". She added, "You see, he doesn't really look like a baby, he looks as though he would *feel* like a baby; I have an image at my finger tips of stroking a baby's cheek and ear." As illustration of her naturally occurring tactile-auditory synaesthesia we may quote: "A trumpet sound is the feel of some sort of plastics; like touching certain sorts of stiffish plastic cloth—smooth and shiny—I felt it slipping."

EXPERIMENTAL SYNAESTHESIA

Since the latter part of the last century it has been well known that administration of mescaline frequently produces synaesthesia. The following instances were obtained in a series of experiments involving doses of 0·3 to 0·5 grams of mescaline. Four subjects provided the examples: the two writers, neither of whom is normally synaesthetic; our colleague E.D.F. who does occasionally experience visual-auditory synaesthesia with certain kinds of music; and S.F., a visiting psychologist, who frequently experiences synaesthesias. The data are of interest in three respects: (*a*) They illustrate the possibility of experimentally producing synaesthesia in subjects not normally given to the phenomenon; (*b*) They represent empirical instances of certain of the other theoretically possible kinds distinguished above; and (*c*) In those who are normally synaesthetic, mescaline seems to augment the vividness of their experiences. Mescaline experimentation, therefore, widens the possibilities of an individual's experience. It may also produce instances of types that do not occur naturally at all. Some of the theoretically distinguished kinds of synaesthesia must be extremely rare; it is of interest to examine their characteristics.

Synaesthesias of the familiar visual-auditory kind occurred with all four subjects, and in all of the three experiments on the second writer (six experiments in all are cited). One subject (P.McK.; 0·3 grams mescaline) was presented with standard auditory tones of known frequency. He reported: "A rather trivial intrusion of a jet of colour upon the primarily uncontrolled imagery of a really impressive kind that was going on. The jet of colour appeared in the field nearest the actual location of the microphone from which the noises came." Two other instances of visual-auditory synaesthesia merit description as they represent a sort of synaesthetic commentary on the size distortions to which mescaline may give rise. With 0·5 grams of mescaline the same subject heard some of the experimenters talking in the next room. Their voices were heard very softly: to synaesthetic thinking they were very "small". He experienced "microscopic kind of imagery" of a visual kind in response to these auditory stimuli. Later in the evening of the same day piano music was played to him by one of the experimenters. The subject reported vivid visual imagery of tiny toy boxing gloves, playing on the key-board of a piano.

Several instances of visual-kinaesthetic synaesthesia occurred during the experiments. Thus, with 0·4 grams of mescaline, L.S. experienced the illusion of greatly increased weight of the cup from which she was drinking during lunch. Vivid visual images of shapes and colours occurred; they accompanied, and had reference to, the act of lifting the cup and the experienced sensations of heaviness. Both L.S. and E.D.F., each with 0·4 grams of mescaline, experienced visual-kinaesthetic synaesthesias when ascending in a lift after lunch. The imagery in both cases was of shapes and colours, and appeared to be somewhat similar:

E.D.F. described it as "like a firework display" and L.S. as "like a fountain". The retrospective report of L.S. was as follows: "Kinaesthetic feeling of being caught in a fountain—trapped in the water and being shot off at the top. Accompanying that, quite distinct image of a fountain. The water was coloured and the sunlight was shining through the water giving it all the colours." In the second experiment of the series, P.McK. experienced a visual-kinaesthetic synaesthesia while being driven in an experimenter's car. The movement of the car was experienced in the following way: "I seemed to be travelling through a thick ocean of air. I felt and saw the pressure of this against me very much as one might feel and see the water passing as one swims through it . . . I passed through strong jets of air that I was able to see and feel."

The term "taste", as used in ordinary speech, is admittedly imprecise. The next experience reported is better described as synaesthesia of the visual-tactile kind than as visual-gustatory. The subject (P.McK.: 0·4 grams mescaline), was given a lifebuoy-shaped peppermint to suck. He reported: "It seems very large—so do teeth. Vivid image of huge tooth—like a Walt Disney cartoon—and a huge lifebuoy. Could be a scene from a cartoon." The size-distortion process again operated, and was an important factor in the imagery experienced. The subject reported retrospectively that the images were like scenes from a cartoon portraying the adventures of a small animal in the mouth of a large animal. It was a kind of Jonah-and-the-Whale theme, treated as Walt Disney might have treated it.

Another instance was described by S.F.—a visual-tactile experience. With closed eyes, she was asked to feel the top of a baize-covered table. "It feels as if it were coloured," she remarked. "It feels a very dark brown, and it feels very, very deep, as though you were feeling over the top of a forest." On subsequent interview, she further described it as, first, a visual image of a patch of dark, dark brown; this was followed by a second visual image of tree-tops, "with a sort of hand feeling over them". It is of interest to note a comment made on the following day by the subject: "My hands didn't really stop feeling all day."

A case of naturally-occurring synaesthesia involving the olfactory sense has been instanced above. A different type, visual-olfactory, occurred during the experiment with L.S. (0·4 grams mescaline). Olfactory stimuli from the Crocker Standards were used. On presentation with one of these she reported, "an immediate, very vivid image of lavender bathsalts in a cheap Woolworth jar". She located the image as that of a jar which had lain in her home for years. When presented with another of the standard olfactory stimuli she experienced visual imagery, this time of "deep pine forests". Although neither lavender nor pine-essence was used, the images were in both cases on the whole appropriate to the general character of the olfactory stimuli presented. During the experiment on S.F. (0·4 grams mescaline), further instances of the visual-olfactory type were described. In addition, the subject experienced those of a tactile-olfactory kind. Given acetic acid to smell, she described it as "A bright yellow smell . . . as if it were sharp crystals of something". Cod-liver oil was experienced as, "a slimy feel and yellow look".

The same subject experienced synaesthesias of a tactile-visual and tactile-auditory nature which she described as being of "the same order as" her ordinary synaesthesias, but "much more vivid and definite". On being asked to look at the green-painted door of the room, she remarked, "It feels as though it were made of green chiffon . . . or like rubber against my fingers". Later, listening to a piano played by one of the experimenters, in which he deliberately ranged over the whole key-board, she described the experience in the following words: "This is a piano with a plushy sort of texture." (Of higher notes): "It would be smooth cloth when you get up there"; (To the top octaves): "Now it's a rather nasty plastic with no surface to it at all." She subsequently confirmed experiencing definite tactile imagery.

In our series of experiments we have so far elicited two instances of synaesthesias involving temperature: the one, visual-thermal, the other thermal-visual. In the first, the subject (E.D.F.: 0·4 grams mescaline) was touched on the left side of her face with a piece of cold metal. Visual imagery was experienced, and took the form of a multiple repetition of swallow-shaped birds, or curved brackets (} } }). These moved from left to right but disappeared when they reached an imaged line which vertically divided her visual field. Immediately after the imagery had been described and drawn, the subject was asked to describe the sensation, which was reported as "coldness". The bird-shaped, or bracket-shaped, objects appeared with this stimulus, and the subject was impressed by their unexpected disappearance when they reached the central part of her closed-eyed visual field. The second, the thermal-visual synaesthesia, occurred during the experiment with S.F. While looking at one of the experimenters, and talking about him, she experienced marked tactile and thermal images: "He feels soft—you know the way a baby is soft—a surface softness with hardness underneath. There's a certain amount of temperature—warm, not cold."

Two of the four subjects experienced visual imagery with pain (P.McK., 0·4 grams mescaline, and S.F., 0·4 grams). The latter, with closed eyes, was pricked with a sharp instrument on her hands, arms and cheek. She described the imagery in the following way: "I've got concentric circles like round the top of a radio mast. As you touch me, jagged things shoot up, little sort of jagged things shooting out from a centre." On immediate questioning she located the visual images as "situated" somewhere between the point of stimulation with the sharp point (arm, hand, etc.) and her closed eyes. To verify that the experience was visual-algesic and not visual-tactile, one of the experimenters gently touched the subject (still with closed eyes, and unaware of what stimulus to expect) on the forehead, cheek, ear and arm with a cool, smooth glass tube. This did *not* produce a repetition of her former imagery, nor, indeed, any imagery whatsoever. Other synaesthetic experiences occurred during the various experiments; all, however, fall into the synaesthesia-type categories represented by the examples which have been quoted.

Finally, we should note one type of experimentally-produced synaesthesia mentioned in the literature, which so far we have not ourselves encountered. This, an algesic-auditory synaesthesia, occurred with mescaline to one of Beringer's subjects, who experienced pain and visual images on hearing the experimenter play the concertina. The pain assumed the form of "luminous curves in the spiral turns of his body", the lower part of his body being "a green varnished cone with spiral windings". (Quoted Klüver, 1942.)

THE PROBLEM OF COMMUNICATION

Very few of those who have taken mescaline or lysergic acid experimentally are likely to regard their experiences as easy to communicate. However consciously co-operative the subject may be, his communications tend to be unsuccessful. One of our subjects reported, in a note written during the experience, that his difficulty arose both from a weakened capacity to communicate, and from a sense of having something unusually complex and significant to convey. Among the sources of difficulty of communication noted in our own series of (to date) eight mescaline experiments and one lysergic acid experiment are the following: (1) Blockage—absence of associations; (2) "Sub-vocal flight of ideas"—too many associations occurring at once; (3) "Mental ataxia"—the subject tries to communicate but there is a discrepancy between what he says and what he means to say; (4) Excessive introversion—the subject becomes so pre-occupied with his images and hallucinations that he neglects to communicate at all; alternatively he may *think* he has done so when in fact he has said nothing; (5) "Mystical thinking"—vague statements about "Time", "Reality", "Truth", etc. Some, but certainly not all subjects react thus. Such thinking figures prominently in the recent book by Huxley (1954), in which he describes his own mescaline experiences: it is scarcely a vehicle for scientific communication. These difficulties of communication we found could be reduced by an agreement about the use of pre-arranged terms like the five listed above. Similarly, previous agreement on the classification of sub-types of synaesthesia facilitated communication of this particular aspect of the mescaline experience.

SUMMARY

A convention for naming the sub-types of synaesthesia is suggested. This throws into sharper relief the theoretically possible kinds of synaesthesia. "Synaesthetic description" is distinguished from synaesthesia proper. The main part of the paper deals with empirical instances of some of the theoretically possible types distinguished. These are taken from the literature, from reports of naturally occurring synaesthesia, and from a series of our own experiments with mescaline. Among naturally occurring synaesthesias, that of the visual-auditory type is overwhelmingly the most common. The paper describes instances of thirteen different kinds of synaesthesia; these include seven induced by mescaline, but not reported as occurring naturally among our subjects. It has been noted that synaesthesia is a very frequent phenomenon of mescaline intoxication. In view of vigorous research interest in mescaline and similar substances, it seems appropriate to reconsider the possible types of synaesthesia.

ACKNOWLEDGMENTS

We acknowledge the help of our colleagues, members of the Mental Health and Psychology Departments of Aberdeen University, with whom we are working on a series of investigations with mescaline and lysergic acid diethylamide. The other members of this research team are: Dr. J. Amor Ardis, Miss Elizabeth D. Fraser, James Drewery and James King. We are also grateful to Dr. Max Valentine for much helpful advice throughout the experiments.

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CLINICAL OBSERVATIONS ON SUXETHONIUM IN E.C.T.

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BECAUSE of their rapidity of onset, brevity of action and relative safety, the choline succinic ester derivatives, in the last two years, have almost completely superseded tubocurarine, gallamine and decamethonium as muscle relaxants in electroplexy. The literature now contains a number of reports of prolonged respiratory arrest associated with the use of these new relaxants. In publishing the results of early experience at Long Grove with three of the new compounds, Monro *et al.* (1953), tended to favour Scoline with thiopentone in a body-weight dosage using a one-syringe technique. The infrequent occurrence of excessive apnoea proved to be no great problem and was easily dealt with. However, during subsequent work in the same hospital, we were impressed by the markedly more abrupt action of suxethonium (Brevidil "E") and felt that further investigations into its clinical properties might yield some reward.

Our aim was to devise a method of protection in E.C.T. that would enable us to treat every patient in need of it with the assurance that the procedure was virtually without danger or discomfort. In a hospital of 2,400 beds, with a large and rapidly increasing turnover, it was thought desirable that the method used should, as far as possible, comply with the following conditions:

(*a*) The time of each treatment should not be unduly increased beyond that required for unmodified E.C.T.

(*b*) The technique should be simple and strictly accurate individual dosage unnecessary.

(*c*) As little extra strain as possible should be put on the nursing staff in the way of preparation, sterilizing syringes and the like.

(*d*) The patient should have no memory of distress associated with the procedure.

With these criteria in view, we tried various modifications of technique and dosage and, as a result, arrived at the following general conclusions regarding the properties of suxethonium:

(*a*) In all patients in sound bodily condition, increase of dosage up to 50 per cent. above the optimal relaxant dose caused no corresponding prolongation of the period of apnoea.

(*b*) It was markedly quicker in onset and briefer in duration of action than the suxamethonium compounds and, in adequate amounts, equally reliable.

(*c*) Concentrated solutions acted more rapidly than dilute and, similarly, rapid injection produced quicker and more profound results than slow injection. This may help to explain why we found that, when mixed with thiopentone, Brevidil "E" exhibited a slower, less abrupt onset than when administered alone. The mixture, too, tended to have a more prolonged action than the relaxant by itself. It may be relevant here to point out that the drug is destroyed by hydrolysis in alkaline solutions and may lose 25 per cent. of its potency in 5 minutes when mixed with thiopentone. This process is accelerated by a rise in temperature.

(*d*) In most cases where the combined injection was used, the effects of the relaxant became evident before those of the barbiturate, so that patients frequently showed signs of respiratory distress, attempting clutching movements at the throat as though to remove a constricting agent. In approximately 1 per cent. of treatments there was some ill-defined memory of suffocation. A possible explanation is that the time between the injection and the shock was longer than the associated retrograde amnesia. We shall return to this important point later.

Our findings outlined above do not materially conflict with those of Malone and Blayney (1952) and Wolfers (1953).

TECHNIQUES

Early in a series of 2,002 treatments on 341 patients, we evolved the following procedure which, we hoped, might go far towards meeting our requirements:

1/100 gr. atropine was given subcutaneously ¾ to 1 hour before treatment. Suxethonium is supplied as a white, crystalline, readily water-soluble powder in glass ampoules containing 100 mgm. active cation which we dissolved in 2 ml. sterile water. The required number of ampoules of the relaxant and of thiopentone sodium were prepared immediately before commencement of treatment and placed on a trolley together with syringes, No. 14 needles, swabs, spirit, at least two airways, suitable gags, and a tourniquet. Nikethamide was available. Anticholinesterases such as neostigmine are of no value as antidotes to the effects of this group of compounds, and may in fact potentiate them.

The patient lay supine in bed, thorax and abdomen exposed so that respiration could be observed; the head was kept low. 1·5 ml. (75 mgm.) for women, 2 ml. (100 mgm.) for men, were drawn into a syringe followed by 3 ml. 5 per cent. thiopentone and the mixture injected into the selected vein in from 2 to 5 seconds. Muscle fasciculation commenced in from 5 to 10 seconds and was evident first round the mouth and in the neck. Respiratory arrest took place early and was not, we found, a reliable indication of complete peripheral relaxation which, we assumed, was established with the cessation of muscle twitching. With a fast injection this normally occurred in from 10 to 20 seconds. The electrodes were placed in position and a gag put between the relaxed jaws, care being taken that the lips were not pinched between it and the teeth. We found this precaution to be extremely important because direct stimulation of the temporalis causes a short but powerful contraction of that muscle sufficient to damage the unprotected teeth or lips.

No preliminary oxygenation was necessary though we carried it out as an added precaution in the treatment of four patients in poor physical condition. The shock was given 15 to 20 seconds after the injection. The result could only rarely be described as a convulsion and was manifest often by the faintest peri-oral and -orbital tremor. In our experience, the most reliable means of knowing whether an adequate shock had been administered was to feel the patient's fingertips with one's own, when a tremor was evident. We prefer this to possibly more dramatic and certainly more time-consuming methods. The gag could be removed safely and slow, gentle, rhythmic inflation started at the end of clonus. Apnoea was rarely shorter than 1½ and longer than 3 minutes. Recovery was gratifyingly uneventful and most infrequently accompanied by the noisy restlessness so often following "straight" E.C.T. Using this procedure, one doctor, assisted by three well drilled nurses, can carry out 16 treatments in one hour.

Prolonged respiratory arrest was the only troublesome complication encountered in this series and occurred only in four patients, all of whom were in a state of dehydration and semi-starvation due to their refusal to take adequate nourishment. In these cases, apnoea, on the usual dosage, lasted from 4 to 7 minutes. This matter will be considered later. We did not use an airway routinely but found it necessary in a few cases—usually obese, middle-aged or elderly patients. No bony injuries occurred in this series and complaints of muscle pain, headache and malaise were no more common than after unmodified electroplexy. Four patients said they remembered a feeling of suffocation before losing consciousness on a total of seven occasions. Only one of them showed any marked distaste for subsequent treatments.

We have already pointed out that dilution of suxethonium tends to retard and prolong its action. Thiopentone has a central respiratory action which might well potentiate the relaxant's effect on the muscles of respiration. It seemed possible to us that concentrated suxethonium alone with its very rapid onset of action might enable us to administer the shock so soon after the injection that the initial paralysing effect would come within the period of retrograde amnesia associated with electroplexy. Thus memory of the feeling of suffocation might be abolished. And omitting the barbiturate, we hoped, might reduce the possibility of prolonged respiratory arrest. We decided to put this hypothesis to the test and carried out a further series of 1,602 treatments on 267 patients using the following procedure.

100 mgm. suxethonium in 2 mls. of water was, we found, a convenient dilution. Within the comparatively rough limits of dosage required of this drug it is easy to measure the required amount in a 5 or even 10 ml. syringe. This concentration, too, produces optimal results. 1½ ml. (75 mgm.) for females, 2 ml. (100 mgm.) for males, were injected quickly into a suitable vein. In rarely more than 5 seconds muscle fasciculation became apparent and frequently the patient would attempt grasping motions at the throat but, quite dramatically, with the onset of total paralysis, the hands would drop, their purpose unaccomplished. At this juncture, between 5 and 10 seconds after the injection, the gag was inserted, the electrodes placed in position and the shock administered. As was the case in the previous series, clonus was minimal. In a few cases spontaneous breathing started at the end of clonus; in the majority assisted respiration was required for periods up to one and a half minutes. If excessive cyanosis developed, oxygen was administered during clonus but we carefully avoided over-ventilation, which we found sometimes lengthened both clonus and apnoea. In one case, a man of 77 in poor senile health, apnoea lasted for three and a half minutes, the longest period recorded in this series; subsequent doses of 60 mgm. provided adequate protection in his case with no further excessive respiratory arrest. Apart from the above exception, none of these patients was seriously cachectic.

All sufficiently accessible patients were asked what their last memory was before treatment. A few recalled having the injection but only one remembered a feeling of suffocation. She was an involutional depressive and well in touch.

Although she experienced this presumably distressing phenomenon on eight occasions and benefited considerably, at no time did she show any dread of the treatment. Recovery generally was quieter than after unmodified E.C.T.

It has been suggested that after the administration of this type of relaxant, muscular pain may occur, severe enough to incapacitate the patient for a day or so and that it is advisable to keep the patient in bed during treatment. This has not been our experience and in 1,602 treatments we have had complaints of muscle pain in only two and these not severe enough to interfere with the course of treatment.

Very rarely the depolarizing effect of Brevidil "E" did not manifest itself for up to 15 seconds after injection although the dose given was adequate, as shown by eventual full relaxation. We considered it possible that in such cases circulation time played a part. According to Best and Taylor (1950), some of the causes of lengthened circulatory time are hypertension, myxoedema, polycythemia, and heart failure. Secondary polycythemia may be associated with chronic pulmonary disease, congenital cardiac abnormalities, some forms of heart disease, chronic poisoning with a number of chemicals, and adaptation to the rarified atmosphere of high altitudes. Haemoconcentration due to shock or dehydration could also delay the passage of blood. All our patients who showed a delayed response to the relaxant came within the age group in which hypertension, chronic bronchitis and emphysema and some degree of cardiac decompensation are commonly found. In our first group the four cachectic patients who were most subject to excessive apnoea showed this delayed response to Brevidil "E". Perhaps their apnoea was related to the same mechanism. The drug is said to have a selective action at the skeletal neuro-myal junction and to be rapidly destroyed mainly by serum pseudocholinesterases. A slow circulation time could be associated with a relative stasis at the sites of action of suxethonium. Consequently the slow "turnover" of pseudocholinesterases could delay the inactivation of the relaxant and thus prolong paralysis.

These observations and speculations may help to explain occasional unexpected variations in response to the drug and suggest other lines of investigation.

SUMMARY AND CONCLUSIONS

Two methods of protection in E.C.T. are described. In the first, fixed doses of Brevidil "E" with thiopentone were used; in the second, Brevidil "E" alone. Perhaps it is too early to dogmatize but, nevertheless we are confident that the second method of treatment is safe, rapid, uncomplicated and significantly reduces the risk of prolonged apnoea associated with the use of the newer relaxant drugs. We had none in our series of 1,602 treatments. Because of its simplicity it is as nearly foolproof as possible and demands little extra time and effort from the staff concerned. Complications peculiar to barbiturates such as sensitivity, central respiratory depression, perivenous and intra-arterial injection are avoided. It appears therefore to be a suitable method for a large hospital or out-patient department where E.C.T. has to be given promptly to all patients in need of it, regardless of their bodily state, with the minimum of danger and discomfort. Finally we would like to emphasize three points culled from our experience:

(*a*) Over-enthusiastic ventilation may prolong apnoea.

(*b*) Too early oxygenation during the convulsion in some cases lengthens quite markedly the duration of the convulsion, possibly by reducing cerebral CO_2 tension and thus interfering with the self-limiting action of the fit.

(*c*) A cachectic patient who has initially required a lower than standard dose of relaxant, may, after two or three treatments, when his appetite, and consequently his physical state, have improved, require a larger dose if full relaxation is aimed at.

ACKNOWLEDGMENTS

We are indebted to Dr. A. B. Monro for his encouragement and advice and to the members of the nursing staff of Long Grove Hospital for their assistance during the course of this work.

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MODIFIED LEPTAZOL CONVULSIVE THERAPY

By

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(Received 29 June, 1954)

THE use of chemically induced convulsive therapy introduced by Von Meduna in 1934 was followed by the introduction of electric convulsive therapy by Cerletti and Bini in 1937. The latter method is now of almost universal use. The main reasons for the change over were the elimination of the unpleasant aura experienced in connection with the leptazol fit and the fact that body accidents were said to be less frequent with E.C.T. There does not appear to be any evidence of greater therapeutic efficiency with E.C.T. Bini and Bazzi (1949) in summarizing statistics covering twelve thousand cases, found no difference in the remission rates in the two therapies. Dedichen (1946) indicated that the value of the two therapies in depressions was similar and Ross (1946) found this also for cases of acute excitements.

At this hospital leptazol has been retained in the treatment of psychotic excitements of all types, the clinical impression being that it was quicker and more effective than E.C.T. We were, moreover, loath to forgo the rapid quietening effect in cases of mania and catatonic excitements, and the clinical ease of induction of a fit in ward or sideroom by means of a single injection, as compared with the difficulties attending the use of the apparatus associated with E.C.T. Since the introduction of relaxants in conjunction with E.C.T. in this hospital in 1950, we have continued to use leptazol, but with the growing feeling that we were adding an unnecessary physical risk to the treatment.

Before the introduction of succinylcholine and other brief muscle relaxants, it was clearly impossible to devise a satisfactory technique in which convulsants could be used in conjunction with relaxants, because the waiting period of several minutes between the injection of decamethonium iodide or of the curare derivatives necessitates the use of evipan or pentothal, which are themselves antagonistic to the convulsant action of leptazol. In 1941 Bennett did introduce curare modified leptazol fits without intravenous barbiturates, but the method was abandoned after a few years because of the unpleasant sensations experienced by the patient during the three to four minutes' interval between the injections of relaxant and convulsant, and because, with E.C.T., a barbiturate could be given in conjunction with the relaxant.

With the introduction of suxamethonium and suxethonium compounds, it was thought that it might be possible to devise a technique for modifying the leptazol fit without the need of inducing sleep with barbiturates owing to the extremely rapid effect of these relaxants. Our first attempt was to give an intravenous injection of suxamethonium bromide, wait 20 to 30 seconds, and then inject the leptazol through the same needle which had been left in situ. We obtained well modified fits but the patient experienced, and afterwards bitterly complained of, the feeling of suffocation normally experienced with suxamethonium when unaccompanied by barbiturates, as well as the unpleasant aura associated with leptazol. Following this we tried suxethonium followed after a shorter interval by leptazol, with a consequent shortening of the unpleasant prodromata.

The modification that we have now used for over two hundred treatments and have found effective is to dissolve 50 to 100 mgm. of the active cation of suxethonium bromide in 7 to 12 c.cm. of 10 per cent. leptazol (that is, using leptazol solution as the solvent and not water). This mixture appears to be stable for at least ten minutes, but it is our practice to use the solution immediately. It is injected rapidly, preferably through a number 18 needle, and the resultant fit appears to be as well modified as that seen in modified E.C.T. This appears to be due to the fact that the leptazol convulsion, unlike the electro-convulsion, builds up from a series of clonic jerks to a tonic spasm, giving just that amount of time necessary for the relaxant to become effective. There is none of the "black" cyanosis seen in the straight leptazol fit, although it is just as necessary to oxygenate the patient in the post-convulsive apnoeic period as it is with modified E.C.T. A positive pressure insufflator must be used for this purpose.

Using this technique we have noted that less oxygen is necessary than in the modified E.C.T. and that the patient remains a much better colour throughout, probably due to the fact that leptazol is itself a respiratory stimulant. The patient usually wakes from his fit without showing any undue excitement and often without realizing that he has already had treatment. In a few cases there has been a wild post-convulsive confusional period as sometimes occurs following E.C.T. and for this an intravenous injection of sodium amytal 0·25–0·5 gm. is necessary.

We have timed the length of the fit and of the post-paroxysmal apnoea in 70 leptazol treatments and made recordings of the B.P. before and immediately after the fit in a few cases, using leptazol and E.C.T. alternately. We have also timed the fit and the post-convulsant apnoeic period during 30 E.C.T.s given to some of these patients. There was no difference in the length of the fits induced by E.C.T. and leptazol. The average length of the apnoeic period following a leptazol-induced fit was 52 seconds. The average length of the apnoeic period following an E.C.T.-induced fit was 48 seconds.

There was a greater increase in the B.P. following a leptazol-induced fit than following modified E.C.T. The range of increase in diastolic pressure following leptazol was 0 to 46 mm.; for E.C.T. it was from 0 to 18 mm. mercury. The range of increase in systolic pressure following leptazol was from 36 to 160 mm. of mercury and for E.C.T. from 10 to 70 mm. mercury.

So far we have given treatment to patients with an age distribution of 16 to 75 years and there have been no mishaps.

Atropine gr. 1/50 to gr. 1/75 is injected hypodermically less than one hour prior to the treatment which is usually given in the morning, the patient having been without food for at least three hours. We have found it advisable to deny the patient food or drink for an hour or two following the treatment as otherwise some become nauseated and may vomit. Severe nausea can be effectively prevented by antihistaminics or by 50 mgm. of largactil given with the atropine before the next treatment.

We find that the majority of patients, male and female, are satisfactorily relaxed after 75 mgm. a.c. of the active cation of suxethonium bromide. Elderly patients and small thin women are well relaxed after 50 mgm. a.c. and muscular men may need 100 to 150 mgm. a.c. of suxethonium, although this dose does tend to prolong the apnoeic period by about 30 to 60 seconds.

The dose of leptazol for the average male patient is 10 c.cm. Again, women and elderly patients may need only 7 or 8 c.cm. Occasionally it has happened that a patient has failed to convulse, either because insufficient leptazol has been given or it has not been injected quickly enough, or because sedatives have been given to the patient within the previous twenty-four hours.

To us the most surprising finding has been that, in comparison with the straight leptazol-induced fit and the fit induced by separate injections of suxethonium and leptazol, the combined suxethonium and leptazol injection is associated with much less apprehension and far fewer reports of unpleasant aura. In fact many patients are unable, as after E.C.T., to recall anything after the injection. It has been the practice in this hospital to treat a certain number of schizophrenics with E.C.T. rather than with insulin, the former method of convulsive therapy being used more because of the lessened risk of physical injury than because of any therapeutic advantage over leptazol. In fact from our early experience of leptazol prior to the introduction of E.C.T. we are inclined to believe that it is the more effective treatment in schizophrenia. Since we can now modify the convulsions to a similar extent, we are continuing to use it in place of E.C.T.

Because of the simplicity of this method we feel that we have now such a simple technique for inducing therapeutic convulsions that it may well be used in place of E.C.T. in the occasional emergency and in situations where the more complicated apparatus of E.C.T. is not readily available. It seems to us also that the anxiety often associated in the lay mind with anything connected with electricity often deters our patients from accepting E.C.T. We refer particularly to psychoneurotic depressions.

Summary

A new technique is offered for the employment of relaxants in leptazol-induced convulsion therapy.

A comparison of this method with relaxant-modified E.C.T. is described.

Acknowledgments

We wish to thank Dr. R. Ström-Olsen, Physician Superintendent, Runwell Hospital, for permission to publish.

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THE EFFECT OF CONVULSIVE THERAPY ON PLASMA ADRENALINE AND NORADRENALINE

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It is generally assumed that an activation of the sympathetic system plays an important part in the therapeutic efficacy of convulsive treatments, be it as an unspecific result of stress or owing to a more circumscribed stimulation of specific centres in the hypothalamus and elsewhere. Such an effect has been postulated on the basis of various changes observed after convulsions, such as a rise in blood pressure (Accornero, 1940; Bini and Puddu, 1940; Piette, 1950), hyperglycaemia (Castelluci, 1940; Kessler and Gellhorn, 1941), leucocytosis and lymphocytosis (Gellhorn and Frank, 1948, 1949; Michael, 1949) and eosinopenia (Altschule, Parkhurst and Tillotson, 1949). Pupillary dilatation and contraction of the nictitating membrane have been described in cats (Gellhorn and Darrow, 1939). More direct evidence is provided by the finding that the adrenaline stores of the adrenal medulla are decreased after electrically produced convulsions (Pekkarinen, Hakala and Hyppönen, 1952).

An increase of the adrenaline concentration of peripheral blood in animals and humans following electrical stimulation has also been described (Hann and Kinzius, 1949; Tietz and van Harreveld, 1949; Kinzius and Hann, 1951), but the methods used were lacking in specificity as shown by the fact that the basal values were reported to be up to 2,000 times higher than those now considered probable. The significance of these results therefore cannot be accepted, particularly since we have been unable to confirm the claim of Lehmann and Kinzius (1951) that plasma contains an inactive, protein-bound precursor of adrenaline (Weil-Malherbe and Bone, 1954). Since a reliable and, as we believe, specific method for the estimation of adrenaline and noradrenaline in plasma is now available, the effect of various forms of convulsion treatment on the plasma level of these amines has been investigated. The introduction of muscle paralysants into convulsion therapy, with or without the use of anaesthetics, raises the question of how these modifications affect the sympathetic response. Electrical convulsions were therefore produced (1) without modification ("straight E.C.T."), (2) after barbiturate administration and (3) after the injection of both barbiturate and paralysant. Similarly the effect of leptazol convulsions was studied (1) without modification and (2) after the injection of a paralysant agent.

EXPERIMENTAL

Methods

Electrical convulsions were produced by the application of 90–120 V. for 0·4–0·5 sec. in the usual way.

5–Cyclohex–1–enyl 1,5–dimethylbarbituric acid ("hexobarbitone") was injected intravenously in doses of 0·2–0·3 g.

5–Pentamethylene tetrazol ("leptazol") was injected intravenously in doses of 7–12 ml. of a 10 per cent. solution.

Bis–2–dimethylaminoethylsuccinate bis–methobromide ("suxamethonium bromide", "brevidil M") was injected intravenously in doses of 20–30 mg. of active cation. It was usually mixed with the hexobarbitone solution in the syringe immediately before the injection.

The corresponding bis–ethobromide compound ("suxethonium bromide", "brevidil E") was injected intravenously in doses of 55–75 mg. of active cation. For use in "modified leptazol therapy" (Berrington and Goldin, 1955) it was mixed in the syringe with, usually, 10 ml. of 10 per cent. leptazol solution immediately before injection.

Venous blood samples (15 ml.) were collected as previously described (Weil-Malherbe and Bone, 1952a). The haematocrit value was determined by centrifugation in Wintrobe tubes at about 2,000 *g* for 45 min. Adrenaline and noradrenaline were determined in plasma by the differential fluorimetric method (Weil-Malherbe and Bone, 1953).

Results

1. *Electroshock*.—The investigations were done on 13 subjects, 10 men and 3 women, all schizophrenics either hitherto untreated or untreated for several months previously. Each patient was submitted in turn to all three forms of treatment at intervals of about 1 week. The three series of results were thus obtained on an identical sample of patients and are strictly comparable. In the first series "straight E.C.T." was used, in the second the current was applied 1–2 min. after the injection of hexobarbitone and the treatment of the third series was "modified E.C.T." as used routinely in this hospital, in which the current is administered 1–2 min. after a combined injection of hexobarbitone and brevidil M. In the last form of treatment one or two oxygen insufflations were given in the interval between injection and stimulation and again after the termination of the fit.

Four blood samples were collected during each treatment, 2 before and 2 after the fit. In the first series ("straight E.C.T.") the first 2 samples were withdrawn with an interval of about 10 min.; a measure of spontaneous variation is thereby provided. In the other two series the first sample was withdrawn before, and the second about 1 min. after the injection, but before the application of the current. The third sample was collected as soon as twitchings or convulsions had ceased and the last sample about 10 min. later.

Fig. 1 shows the mean percentage concentration changes observed in the three series. In straight E.C.T. the plasma adrenaline concentration rises by $75 \cdot 5 \pm 8 \cdot 5$ per cent. above the base level immediately after the fit; 10 min. afterwards it has almost returned to the starting level. The second sample of this series does not differ from the first, indicating the absence of spontaneous change within a similar period of time. The second sample of the other two series shows, within the very short time interval between the injection and the withdrawal of the sample, a remarkable reduction of the adrenaline level amounting to about 60 per cent., although the degree of anaesthesia attained was usually very superficial. The application of the current reverses this effect. The increase above the initial value observed directly after the fit is only slightly below that found after straight E.C.T. The difference from series 1 is not significant for the second series, whereas it is significant at the 5 per cent. level of probability for the third series (Table II). Within 10 min. after the fit the adrenaline concentration has dropped to a value slightly below the base line indicating the persistence of some degree of sedative action. The difference from series 1 is significant in both cases. Measured by the difference between samples 3 and 4 the height of the adrenaline concentration peak is about equal in all three forms of treatment.

The noradrenaline concentration of plasma, like that of adrenaline, is significantly raised by straight E.C.T. immediately after the fit and is still elevated 10 minutes later. The increase of the noradrenaline level, though still significant, is much reduced when hexobarbitone is administered, and it is no longer significant when hexobarbitone and brevidil M are combined (Table I). In contrast to the dramatic depression of the plasma adrenaline level

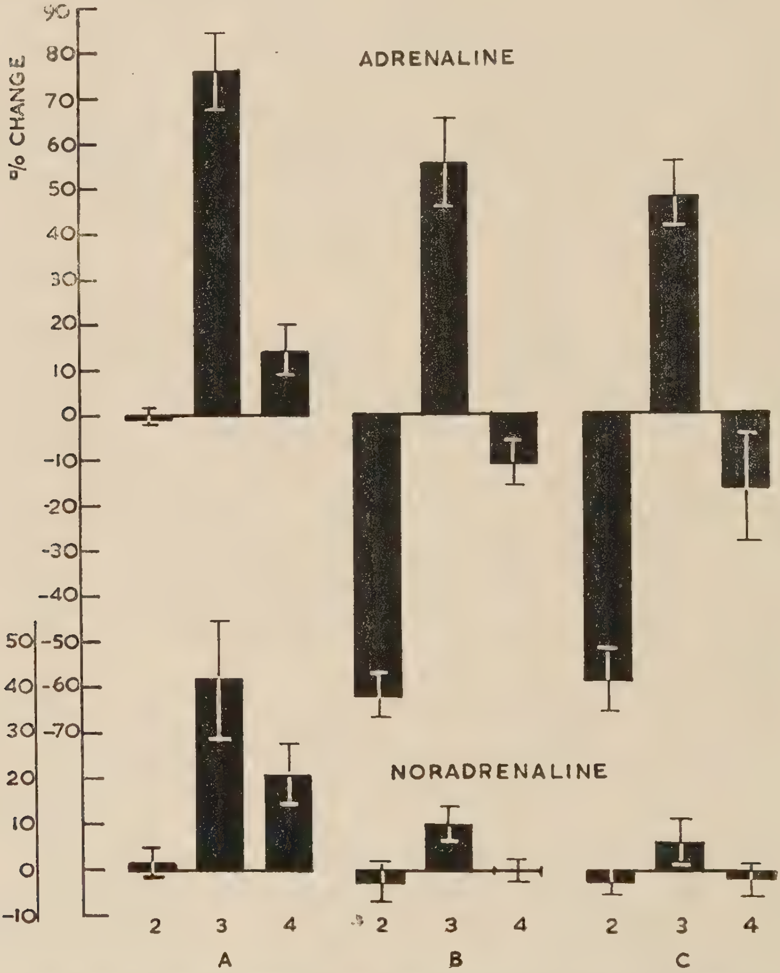

FIG. 1.—The effect of various forms of electroshock on the concentration of adrenaline and noradrenaline in plasma.

The bars indicate the mean percentage concentration changes in samples 2, 3 and 4 of each series. The barred lines indicate the standard error of the mean. A = unmodified E.C.T.; B = E.C.T. after hexobarbitone injection; C = E.C.T. after combined injection of hexobarbitone + brevidil.

Initial values (in μg./1 of whole blood):

	A	B	C
Adrenaline	1·51 ± 0·089	1·47 ± 0·085	1·35 ± 0·093
Noradrenaline	3·77 ± 0·22	4·00 ± 0·155	4·01 ± 0·135

by the injection of hexobarbitone the fact is of interest that the noradrenaline concentration in sample 2 remains unaffected whether the barbiturate is injected alone or in combination with brevidil.

TABLE I

Significance of differences between means of samples from the same series

Samples compared	"Straight E.C.T."		E.C.T.+ Hexobarbitone		E.C.T.+ Hexobarbitone +Brevidil		Leptazol		Leptazol +Brevidil	
	A	N	A	N	A	N	A	N	A	N
1 v. 2 ..	–	–	+	–	+	–	–	–	–	–
1 v. 3 ..	+	+	+	+	+	–	+	+	+	–
1 v. 4 ..	(+)	+	–	–	–	–	–	(+)	–	–
2 v. 3 ..	+	+	+	(+)	+	–	+	+	+	–
2 v. 4 ..	(+)	(+)	+	–	+	–	–	(+)	–	–
3 v. 4 ..	+	–	+	(+)	+	–	+	–	+	–

Symbols: + ~P ≤ 0·01
(+)~P < 0·05 > 0·01
– ~P > 0·05
A = Adrenaline
N = Noradrenaline

The addition of a muscle paralysant to the barbiturate has no significant effect on the response of either the adrenaline or the noradrenaline concentration, compared with the action of the barbiturate alone (Table II).

2. *Leptazol convulsions.*—Two forms of treatment were compared, leptazol alone and leptazol combined with brevidil E. With the exception of 3 cases appearing in both series the subjects of the first series were not the same as those of the second. The cases of the first series (leptazol alone) consisted of 8 male and 1 female schizophrenics and 3 male manic patients, a total of 12. In the second series (leptazol+brevidil E) there were 7 cases of schizophrenia, 2 of mania and 1 of depression, all males, a total of 10. In both series the first 2 blood samples were collected before the injection, with a 10-minute interval; no significant change of the adrenaline or noradrenaline level was observed within this period. The third blood sample was collected immediately after the

TABLE II

Significance of differences between means of corresponding samples from different series

Series compared	Sample 2		Sample 3		Sample 4	
	A	N	A	N	A	N
"Straight E.C.T." v. E.C.T.+hexobarbitone ..	+	–	–	(+)	+	+
"Straight E.C.T." v. E.C.T.+hexobarbitone+brevidil	+	–	(+)	(+)	(+)	+
E.C.T.+hexobarbitone v. E.C.T.+hexobarbitone +brevidil	–	–	–	–	–	–
"Straight E.C.T." v. Leptazol	–	–	+	–	–	–
Leptazol v. Leptazol+brevidil	–	–	–	+	–	(+)
E.C.T.+hexobarbitone+brevidil v. Leptazol+ brevidil	+	–	+	–	–	–

Annotation as in Table I

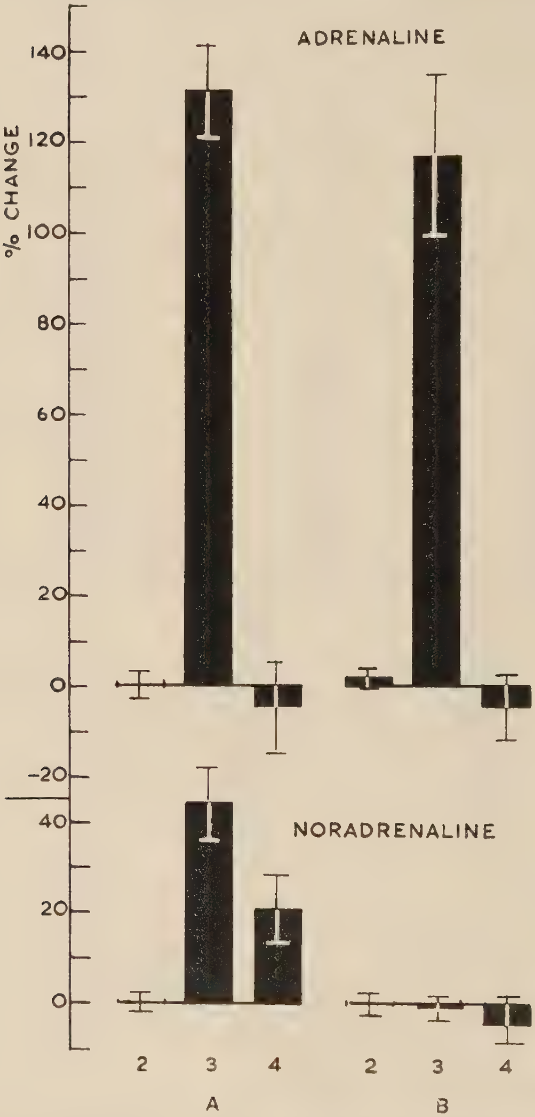

FIG. 2.—The effect of leptazol shock, with (B) and without (A) brevidil, on the concentration of adrenaline and noradrenaline in plasma.

The bars indicate the mean percentage concentration changes in samples 2, 3 and 4. The barred lines indicate the standard error of the mean.

Initial values (in µg./1 of whole blood):

	A	B
Adrenaline	1·49±0·080	1·56±0·084
Noradrenaline	4·20±0·127	4·39±0·189

fit, the fourth 10 minutes later. When brevidil was added to leptazol, one or two oxygen insufflations were given after the fit.

The rise of the adrenaline concentration after the fit is almost twice as great as after E.C.T. The effect disappears within 10 minutes. In one experiment brevidil E was replaced by the longer-acting brevidil M; it was injected alone, a blood sample was withdrawn immediately afterwards and finally the leptazol injection was given. Although barely 1/2 min. elapsed between the first injection and the collection of the blood sample, the plasma adrenaline level was found to be decreased by 45 per cent.; the noradrenaline level was unaffected. The procedure caused considerable distress and apprehension and was therefore not repeated.

The injection of leptazol alone produces a rise of the plasma noradrenaline level which closely corresponds to that following straight E.C.T. Ten minutes later the noradrenaline concentration is still significantly above the basal level. This effect on the noradrenaline concentration completely disappears when leptazol is combined with brevidil E. The suppression of the noradrenaline response can therefore be achieved not only with hexobarbitone, or with hexobarbitone+brevidil, but also with brevidil alone.

DISCUSSION

When the physiological or therapeutic effects of convulsive therapy are considered, it is customary to distinguish between primary and secondary effects, i.e. between those directly connected with the convulsive discharge of groups of neurons and those dependent on the reactions to, or sequelae of, the nervous discharge, such as muscular contractions, cardiovascular changes and anoxia. In the recent modifications of convulsive therapy the secondary effects are minimized by the use of paralysant drugs and artificial respiration without impairment of the curative action. It has been shown in this investigation that, while the increase of the plasma noradrenaline concentration is clearly the result of secondary effects and is suppressed with them, the rise of the plasma adrenaline concentration persists. It therefore seems reasonable to assume that it is due to the stimulation of autonomic centres in the brain. An increased discharge of adrenaline may thus be a component of the therapeutic mechanism, while an increased discharge of noradrenaline is without significance in this respect.

The increase of the plasma adrenaline level is of the characteristic fleeting form associated with the action of adrenaline after intravenous injection. The increased discharge of adrenaline is therefore brief and probably lasts only for the time during which the current flows. Adrenaline estimations carried out on the plasma of patients treated with subconvulsive impulses have shown that the maximum concentration is usually reached while the current is flowing and that the effect has considerably subsided already 1 minute after the interruption of the current (Weil-Malherbe and Bone, 1952b). It is possible therefore that the effect here described was not observed when it reached its peak.

It is of interest to evaluate separately the modifications of the plasma adrenaline and noradrenaline levels by hexobarbitone alone, brevidil alone and by both combined. The rise of the noradrenaline level is as completely suppressed by brevidil alone as by brevidil+hexobarbitone, while hexobarbitone is not quite so efficient in this respect. It is likely therefore that the discharge of noradrenaline is mainly connected with the tonic phase of the convulsions which is inhibited by barbiturates and, to a smaller extent, with the clonic phase which is not.

The reduction of the plasma adrenaline level which so closely follows the intravenous injection of hexobarbitone is also observed after the injection of other barbiturates, such as sodium amytal (unpublished observations) or pentothal. The latter drug, in a dose of 0·75 g., was used in a series of treatments investigated with Dr. J. D. Montagu (cf. Montagu, 1954); it led to a mean reduction of the plasma adrenaline level by 64·1±2·9 per cent. and of the noradrenaline level by $12 \cdot 5 \pm 3 \cdot 6$ per cent. (19 observations). The effect is thus probably common to all barbiturates and, indeed, to anaesthetics generally, as shown by preliminary observations on patients undergoing various forms of anaesthesia. These and other observations (cf. Weil-Malherbe, 1954) suggest that the activity of the subcortical autonomic centres is geared to the activity of the cortex and that a depression of the latter entails a depression of the former. Some authors, such as Himwich (1951) and Gellhorn (1953), have put forward the opposite view assuming that the cortex inhibits the activity of the centres governing the discharge of adrenaline and that the regression of cortical dominance is coupled with a release of adrenaline. Our results do not support this theory.

Summary

The effect of convulsive treatments on the concentration of adrenaline and noradrenaline in plasma has been investigated. Electroshock was applied (1) without modification, (2) after the injection of hexobarbitone and (3) after a combined injection of hexobarbitone and brevidil ("succinyl choline"). The effect of leptazol was studied (1) without modification, (2) when combined with brevidil.

The unmodified electroshock produces an increase of about 75 per cent. in the plasma adrenaline concentration immediately after the fit; it subsides within about 10 minutes. The plasma noradrenaline concentration is raised by about 40 per cent.; this increase decays more slowly. The injection of hexobarbitone or of hexobarbitone + brevidil leads to a fall of the plasma adrenaline concentration reaching about 60 per cent. within 1 minute. The application of the current reverses this effect, producing a rise of the plasma adrenaline level which is only slightly below that found after an unmodified electroshock. The rise of the plasma noradrenaline concentration is completely suppressed after the injection of hexobarbitone + brevidil, and almost completely after that of hexobarbitone alone.

The injection of leptazol is followed by a mean increase of the plasma adrenaline level amounting to over 130 per cent. The noradrenaline response is similar to that observed after unmodified electroshock. The addition of brevidil does not significantly change the effect of leptazol on the plasma adrenaline concentration, but it completely abolishes the rise of the noradrenaline concentration.

Acknowledgments

The author wishes to express his appreciation for the eager co-operation of his clinical colleagues, especially of Dr. S. Goldin and Dr. A. Kirkland. Grateful acknowledgments are due to Mr. A. D. Bone for expert technical assistance and to the Medical Research Council for a grant in aid of technical assistance.

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A CONTROLLED STUDY OF THE EFFECT OF MEPHENESIN ON PSYCHIATRIC OUT-PATIENTS

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INTRODUCTION

THE chemical compound 3–ortho–toloxy–1, 2–propanediol, known as mephenesin, Myanesin or Tolserol, was shown by Berger and Bradley in 1946 to depress reflex excitability of the spinal cord and to have a depressant action at higher levels of the central nervous system in higher dosage. Other investigators confirmed this and the drug has been found effective for the spasticity and tremor of some neurological conditions.

The use of mephenesin in psychiatric conditions has been reviewed recently in this journal (Ewing and Mendenhall, 1953). In brief, there have been many reports of benefit in neuroses and psychoses with anxiety, tension and agitation; but results have been inconstant and their proper assessment made difficult by the absence, with two exceptions, of controls. Both studies in which controls were used were limited to alcoholic or post-alcoholic states; in one (Herman and Effron, 1951) it was reported that myanesin was of decided benefit; in the other (Ewing and Mendenhall) it was found to be of little value.

PROCEDURE

The present study was carried out with 24 out-patients, 17 women and 7 men. Their ages ranged from 18 to 57 but a large majority were in their thirties or early forties.

Criteria for selection of these patients were as follows:

(*a*) Anxiety present with some manifestation of somatic motor tension such as tremor, restlessness, subjective complaint of tension.

(*b*) No other treatment of any kind being received.

(*c*) Patients living within convenient travelling distance of the hospital.

(*d*) Patients with very low intelligence excluded.

(*e*) Women with pre-menstrual tension states excluded.

(*f*) Patients with obvious exogenous variables, such as intermittent domestic discord, excluded.

(*g*) Patients with prominent hysterical features such as exaggeration or exploitation of symptoms excluded.

None of the group had any psychotic features. In most, the basic personality was anankastic (i.e. strong affects, ambivalence, over-conscientiousness and scrupulousness, obsessive rumination, etc.); this probably contributed to these patients' co-operativeness and reliability as witnesses.

Three substances were given to each patient, all in the form of powder in gelatine capsules which looked identical. These were amytal (gr. 1/3 per capsule), lactose (gr. 7½ per capsule) and mephenesin (0·5 G. per capsule). Two capsules were taken four times a day before food so that the daily dose of amytal was 2⅔ gr. and of mephenesin 4 G.; this dose of mephenesin is about twice that given in most other therapeutic experiments.

The study of each patient was divided into 6 periods over 3 weeks; the periods were Monday–Tuesday–Wednesday and Thursday–Friday–Saturday; on Sundays sodium amytal gr. 1 t.i.d., a.c., was given in tablet form. Each substance was given for two periods.

The boxes of capsules were marked A, B, C by a hospital dispenser who alone knew which was which. The order of administration varied for different patients and, being fixed by other members of the staff, was unknown to the assessing psychiatrist. The orders were so arranged that each substance was given once in the first three periods and once in the last three. No substance was given for two contiguous periods. Not all the orders were regular (e.g. CABCAB) lest later assessments be biassed by the pattern of the patient's earlier responses. The orders were so arranged that in the total of 24 first periods there were 8 administrations of amytal, 8 of lactose and 8 of myanesin; and so for all the other periods, lest a difference in response to the various substances be complicated by a difference in response at various stages of the three weeks' investigation.

All patients were told in the beginning that they were to be given a new medicine, but one which was an improvement on older treatments in only a minority of patients. They were told that the most suitable dose varied for different patients and that 6 different doses were being given to see which, if any, helped them. They were warned that they might feel better in none or only one or two of the periods and much as usual during most periods. No possible side-effects were mentioned. The patients were told that it was most important that doses be taken regularly; if one was missed, they were to double the next dose. At every interview they were reminded that no steady improvement was to be expected.

This routine seemed best suited to produce a discriminating attitude in the patient. They were not told that there were 3 different substances of which one at least was ineffective lest they objected to the idea of being "experimented on" or introduced experimental variations of their own. The explanation given also justified repeating the same form of enquiry at each interview.

All assessments were made by the same psychiatrist at the same time on Wednesdays and Saturdays. At each visit the next period's supply of capsules was given. The patient was asked for a general comment on how he or she had felt for the previous couple of days and that day. A brief enquiry was then made about each of the following items:

Physical Symptoms: headaches, dizziness, visual disturbances, palpitation, sweating, loss of appetite, dyspepsia (nausea, vomiting, epigastric pain), bowel and bladder symptoms, trembling, physical tension symptoms.

Psychic Symptoms: anxiety, self-consciousness, depression, morbid thoughts (phobias, aggressive urges, rumination), feelings of unreality or depersonalization, poor concentration.

These items were scored as 0, +, ++, +++, ++++ for none, slight, moderate, severe, very severe. This method is too subjective to allow item comparison between one patient and another but at each interview the record forms of previous interviews were so arranged that earlier comment on each item could be seen at a glance and discussed with the patient if need be. The emphasis was always on comparison with previous periods. The patient was then asked to do a Serial Sevens test and finally to sum up his or her condition for that period on a five-point scale:

Very good / good / so-so / bad / very bad

The doctor's impression was recorded separately on a similar scale. Such interviews generally took 10–15 minutes; discussion in any other form was evaded as tactfully as possible, lest it should have a cathartic effect.

RESULTS

The composition of the capsules and the orders of administration were made known to the assessing doctor only after the last interview of the last patient.

For each patient the six periods were ranked from best to worst (I–VI) by various criteria. The distributions for the total of 24 patients are given below.

Firstly, on each record form, the patient's and doctor's summings-up were given a quantitative value by rating "very bad" as four points, "bad" as three points, and so on; this gave Tables Ia and Ib:

TABLE Ia

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	3	10	2	3	2	4
II	4	5	1	7	4	3
III	7	5	4	2	2	4
IV	1	2	5	3	8	5
V	7	2	7	5	1	2
VI	2	0	5	4	7	6

This may be condensed to:

TABLE Ib

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	34	19	19
Worst (IV–VI) Periods	14	29	29

Secondly the pluses for all symptom items, physical and psychic, were added on each record form, and, for each patient, the 6 periods were given another ranking from best to worst (I–VI) on these scores; this gave Tables IIa and IIb:

TABLE IIa

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	5	12	2	2	1	2
II	4	4	2	5	3	6
III	5	5	3	3	6	2
IV	3	1	6	3	6	5
V	5	2	6	7	1	3
VI	2	0	5	4	7	6

This may be condensed to:

TABLE IIb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	35	17	20
Worst (IV–VI) Periods	13	31	28

Thirdly rankings in order of clinical benefit were made by using pluses from "autonomic" items only; dizziness, visual disturbances, palpitations, sweating, loss of appetite, dyspepsia, bowel and bladder disturbances. This gave Tables IIIa and IIIb:

TABLE IIIa

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	6	9	1	3	2	3
II	6	7	2	3	4	2
III	3	6	5	6	1	3
IV	5	2	3	3	4	7
V	3	0	7	4	6	4
VI	1	0	6	5	7	5

This may be condensed to:

TABLE IIIb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	37	20	15
Worst (IV–VI) Periods	11	28	33

Fourthly rankings in order of clinical benefit were made by using pluses from "psychiatric" items alone; self-consciousness, depression, morbid thoughts, unreality, depersonalization and poor concentration; anxiety was not included here as its reporting might have been more contaminated by autonomic symptoms. This gave Tables IVa and IVb:

TABLE IVa

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	3	11	4	2	2	2
II	6	6	2	6	2	2
III	3	1	2	5	7	6
IV	5	1	4	6	5	3
V	5	3	6	1	1	8
VI	2	2	6	4	7	3

This may be condensed to:

TABLE IVb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	30	21	21
Worst (IV–VI) Periods	18	27	27

Fifthly a ranking in order of clinical benefit was made for each patient using the pluses for "tremor" and "tension" alone, since these items might be expected to reflect best the known pharmacological effect of myanesin; this gave Tables Va and Vb:

TABLE Va

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	5	9	0	2	4	4
II	7	6	4	3	2	2
III	2	1	6	4	4	7
IV	3	5	3	5	6	2
V	6	3	4	4	4	3
VI	1	0	7	6	4	6

This may be condensed to:

TABLE Vb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	30	19	23
Worst (IV–VI) Periods	18	29	25

Sixthly, on each record form, the Serial Sevens performance was given a quantitative value by the formula:

$$X=\frac{\text{Number of seconds taken}}{\text{Number of correct responses}-\text{number of mistakes}}$$

A ranking was then made from best to worst (I–VI) performance and this gave Tables VIa and VIb:

TABLE VIa

	First Amytal Period	Second Amytal Period	First Lactose Period	Second Lactose Period	First Mephenesin Period	Second Mephenesin Period
I	2	5	3	4	1	0
II	2	3	3	4	1	2
III	2	2	2	0	5	4
IV	4	1	2	3	1	4
V	1	1	4	3	3	3
VI	4	3	1	1	4	2

This may be condensed to:

TABLE VIb

	Amytal Periods	Lactose Periods	Mephenesin Periods
Best (I–III) Periods	16	16	13
Worst (IV–VI) Periods	14	14	17

The total figures are smaller here as one or more performances of the test in 9 cases was invalidated by interruptions or background noise.

The P levels of significance for the differences in the above condensed Tables were:

TABLE VII

	Amytal/Lactose			Amytal/Mephenesin			Lactose/ Mephenesin		
	All Periods	First 3 Periods	Last 3 Periods	All Periods	First 3 Periods	Last 3 Periods	All Periods	First 3 Periods	Last 3 Periods
Summings-up	<0·01	<0·05	<0·02	<0·01	N.S.	<0·01	N.S.	N.S.	N.S.
All symptom items	<0·001	<0·05	<0·001	<0·01	N.S.	<0·001	N.S.	N.S.	N.S.
"Autonomic" items	<0·001	<0·05	<0·01	<0·001	0·02	<0·001	N.S.	N.S.	N.S.
"Psychiatric" items	N.S.	N.S.	N.S.	N.S.	N.S.	0·02	N.S.	N.S.	N.S.
"Tension" and "Tremor" ..	<0·05	N.S.	<0·05	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Serial Sevens	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

N.S.=not significant at the P=0·05 level.

It will be noted that the levels of significance of differences are consistently higher in the last 3 administrations as compared with the first 3. In two distributions the first amytal periods are better than the second amytal periods above the P=0·05 level; there are no significant differences between the first and second lactose periods, or between the first and second mephenesin periods.

When the orders of clinical benefit (I–VI) based on the summings-up are plotted against the chronological orders of periods (1–6), this gives the distributions shown in Tables VIIIa and VIIIb:

TABLE VIIIa

	First Periods	Second Periods	Third Periods	Fourth Periods	Fifth Periods	Sixth Periods
I ..	0	5	2	5	6	6
II ..	2	4	3	2	7	6
III ..	8	4	1	5	4	2
IV ..	2	2	10	4	3	3
V ..	5	5	5	4	3	2
VI ..	7	4	3	4	1	5

This may be condensed to:

TABLE VIIIb

	First 2 Periods	Middle 2 Periods	Last 2 Periods
Best (I–III) Periods	23	18	31
Worst (IV–VI) Periods	25	30	17

The overall differences in the smaller table are significant at the P=<0·05 level; the last 2 periods show an improvement over the middle 2 periods significant at the P=<0·01 level. When similar distributions were drawn up using all symptom items, "autonomic" items and "psychiatric" items as the basis for the best to worst ranking, all showed a tendency, significant or bordering on significance, to improvement in the last 2 periods as compared with the first 2 or first 4. This tendency was minimal in the distributions based on "tension" and "tremor" items and the Serial Sevens performances.

No significant differences were found when the 24 patients were grouped according to age, sex, intelligence (Mill Hill Vocabulary Scale in 20 patients), total score of pluses and range of response on pluses. Such differences as did exist suggested that older patients, those of higher intelligence and those complaining most were more sensitive to the relative effectiveness of amytal.

The order of benefit of the lactose and mephenesin periods did not seem at all dependent on whether or not they followed an amytal period.

The 144 record forms were finally grouped into amytal periods, lactose periods and mephenesin periods and for each group the pluses for each symptom item were added. This gave Table IX:

TABLE IX

	Amytal Periods	Lactose Periods	Myanesin Periods
Headaches	33	42	44
Dizziness	8	13	16
Visual disturbance	13	15	18
Palpitations	27	39	30
Sweating	18	29	30
Loss of appetite	23	30	30
Dyspepsia	22	26	33
Bowel symptoms	7	8	9
Bladder symptoms	11	12	13
Tremor	23	39	30
Tension	77	101	91
Anxiety	68	83	86
Self-consciousness	38	46	47
Depression	60	72	63
Morbid thoughts	62	66	70
Unreality	11	15	15
Depersonalization	22	29	23
Loss of concentration	45	46	46
Totals	685	841	821

For the column totals the amytal/lactose and amytal/myanesin differences are significant at well beyond the $P=0\cdot001$ level; the lactose/myanesin difference is not significant.

Amytal produced the smallest plus score for every one of the 18 items; it seems to have been most effective for tremor, tension, sweating, palpitations and anxiety but only the first reaches the $P=0\cdot05$ level of significant difference. There are no significant differences between lactose and myanesin either for individual item scores or in their overall distribution between middle and highest plus scores.

Patients had not been warned of specific side-effects but note was made of spontaneous comment on any symptom that a patient regarded as new. During amytal periods, 5 patients complained of drowsiness and 2 of mild griping pains. During lactose periods, 1 patient complained of tiredness. During myanesin periods, 4 patients mentioned drowsiness, 1 dizziness and 1 nausea and headache; 3 others were the only patients who had symptoms severe enough to make them stop taking that lot of capsules; one complained of irritability and forgetfulness; another complained of confusion, dizziness, trembling, loss of appetite and nausea; the other complained of nausea and severe griping pains.

Discussion

Mephenesin seems to give no clinical benefit in cases with anxiety and tension and the fact that the more troublesome side-effects were limited to periods when it was used indicates that it would probably be impracticable to give higher doses.

Table VIa shows that only 4 of the best 2 performances of Serial Sevens were during mephenesin periods as against 14 during lactose periods. This difference is significant at about the P=0·02 level and suggests a retardation effect which may be worth investigating further.

While amytal is shown to be superior to lactose and mephenesin, it should be noted that the condition of the patients in the aggregate was, in general terms, only about 20 per cent. better while they were having amytal than while they were having lactose. Even this estimate may be artificially high, as it is likely that patients interviewed while benefited by amytal would view their condition over the previous two days more tolerantly; this is suggested by the fact that every symptom and not just a majority of symptoms was improved during the amytal periods. It is not clear why the second amytal administration should have been so much more effective than the first. A probable factor was a more hopefully expectant attitude on the part of the patients, it being found that, whatever the criteria for assessing the clinical condition, there was always a tendency, sometimes statistically significant, to improvement in the later stages despite the patients being warned that this was not to be expected. There is little doubt that, if the patients had been encouraged to hope for cumulative improvement, the majority would have reported that the course as a whole gave decided benefit. It is interesting to consider this effect of suggestion in relation to the response of out-patients who attend twice a week for six or more electrical convulsive treatments. Many psychiatrists justify the use of E.C.T. in patients whose presenting symptoms are very largely "neurotic" by quoting an improvement rate of 70 per cent. or more and postulating that this is evidence of an underlying endogenous depression in such cases. Fifteen of the 24 patients in this experiment had been given such a provisional diagnosis initially and had had a course of E.C.T. within the previous six months. Seven had experienced no benefit and 8 had reported slight to moderate benefit, usually for a matter of weeks only. When the clinical orders of benefit (on summings-up) are compared with the chronological order of periods it is found that, for the 7 patients who had felt no benefit from E.C.T., there was no significant relationship; for the 8 patients who had benefited temporarily from E.C.T. there was an improvement in the last three periods significant at the P=0·02 level approximately. This suggests that a patient's report of improvement at the end of a course of E.C.T. is no certain indication that it has been a specific remedy for an occult endogenous depressive process.

Summary

The procedure for a controlled administration of mephenesin, amytal and lactose to 24 psychiatric out-patients is described.

Mephenesin is found to be ineffective for anxiety and tension symptoms. Amytal was found to be significantly superior but limited in its effect.

Some comparisons are made with the response of out-patients to E.C.T.

Acknowledgments

My thanks are due to Professor E. W. Anderson for suggesting this study, to Mr. J. C. Kenna for his comments on the statistics, to Miss B. W. Clegg and Mr. J. B. Lloyd for the dispensary work involved and to Miss P. M. Lockwood and Dr. K. Rawnsley for arranging the courses.

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THE EFFECTS OF MEPHENESIN IN NEUROTIC ANXIETY

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(Received 11 June, 1954)

In 1946 Berger and Bradley showed that mephenesin caused muscular relaxation and, in the same year, Stephen and Chandy (1947) reported that the intravenous administration of mephenesin to human subjects was usually accompanied by a feeling of euphoria and relaxation. The clinical trial of mephenesin in neurotic states associated with tension and anxiety was a natural corollary of these findings. Reports of its efficacy have been conflicting, but this is hardly surprising when a new drug is introduced for the treatment of a common disorder whose natural course may be either chronic or self-limiting, which is subject in a marked degree to apparently spontaneous fluctuations in intensity and on which the effects of suggestion are notorious. The assessment of therapy is made more difficult by the fact that there is no satisfactory objective method of measuring changes in the degree of anxiety; the investigator must either use tests the relevance of which many people will dispute or he must rely on clinical assessment, a subjective judgment very dependent on the skill and experience of the clinician. As Bradford Hill (1951) has stressed, clinical assessment can only be given full weight in a therapeutic trial when the possibility of enthusiasm or scepticism on the part of the clinician is eliminated. Such elimination of bias is best achieved by treating one group of patients with the drug and another group with a placebo, the clinician, nursing staff and patients not knowing to which group any particular patient has been assigned.

In the process of determining the efficacy of a new drug, however, reports of uncontrolled clinical impressions form an essential preliminary phase. If such impressions are on the whole favourable, they will not only suggest the need for controlled trials but will also delimitate the most suitable dosage, period of administration and type of case.

Previous Reports

A survey of the literature dealing with the use of oral mephenesin in states of neurotic anxiety and tension has been made by Ewing and Mendenhall (1953). In addition, the work of Monro and Steadman (1953) must be noted. All these reports concur in finding mephenesin of some value in the treatment of neurotic anxiety, but their favourable impressions have not been confirmed by two controlled studies (Block, 1953; Ewing and Mendenhall, 1953; Mendenhall and Ewing, 1954).

Yet although the investigations of Block and of Ewing and Mendenhall were adequately controlled, each is subject to certain limitations. The number of cases studied by Block was only eleven. Ewing and Mendenhall's cases were all alcoholics; and there is no general agreement among psychologists that the digit-span and the Rorschach–Benn tests can reliably measure a change in degree of anxiety. Again, in these studies each patient received both mephenesin and placebo, a procedure which is open to the theoretical objection that, as it is very difficult to make a placebo tasting exactly like a mephenesin tablet, the patient may suppose that the tablet tasting more unpleasant or more sensational is the "genuine" one and thus be influenced by suggestion. It seems worth while, therefore, to report the results of a controlled study attacking the problem in a different way.

METHOD

The present investigation was planned as a controlled trial to determine whether mephenesin was of use in the routine treatment of neurotic patients exhibiting anxiety and tension as major symptoms. The subjects studied were 59 female patients admitted to a neurosis unit, the only criterion for selection being that the patients should show anxiety and tension as major symptoms at the time of their admission. The patients were treated either by mephenesin g. 1 t.d.s. or by a placebo for a week. The first 19 cases received "Myanesin elixir"* or a placebo mixture; the remaining 40 cases had mephenesin or control tablets, crushed and swallowed with water. Treatment was begun two or three days after admission and a clinical assessment made at the beginning and end of the trial week. In addition, each patient was asked at the end of the week whether she thought the tablets had had an effect on her symptoms. Patients admitted to the trial were assigned either to the mephenesin or to the control group by the hospital dispenser on the toss of a coin, but the physician and ward staff were in ignorance of the composition of these groups (it proved impossible to make a placebo mixture looking indistinguishable from the "Myanesin elixir" and hence for the first 19 cases the ward staff—though not the physician—could have known which patients were receiving the mephenesin). Apart from nocturnal sedation, the patients received no other drug or special treatment during the trial week; all were in the same ward and all received the same basic regime of clinical investigations, occupational therapy and social recreation.

Table I shows the composition of the two groups. A rather higher proportion of young patients came into the mephenesin group, though the difference

TABLE I

Item Analysis of the Groups

	Mephenesin		Control	
	No.	Per cent.	No.	Per cent.
Family History positive for neurosis or psychosis	11	34	8	30
Personality poor	14	44	16	59
Duration of illness:				
Under 1 year	20	62	18	67
1–3 years	8	25	7	26
Over 3 years	4	13	2	7
Diagnostic type:				
Anxiety state	12	37	8	30
Anxiety with depression	17	53	14	52
Anxiety with other neurotic syndrome	3	10	5	18
Age:				
Under 30	11	34	5	19
30–49	16	50	15	55
50 and over	5	16	7	26

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* Confirmation was obtained of the finding of Monro and Steadman (1953) that "all patients experience some definite subjective sensation after taking their medicine"; but as each dose of the elixir contains almost as much alcohol as half an ounce of brandy, the mephenesin may not be the sole cause of this sensation.

is not significant at the 5 per cent. level; any effect this difference might have would presumably favour the mephenesin group. In other respects, the two groups are well matched.

RESULTS

The results are indicated in Table II. There is no significant difference between the mephenesin and the control groups, either clinically or subjectively. Nor was any significant difference apparent when only those patients with good personality or those suffering from "pure" anxiety were considered.

TABLE II

Results

	No. of Cases		Chi Square	Probability
	Mephenesin	Control		
Clinical assessment:				
Improved	12	7	0·4	P>0·5
Not improved	20	20		
Patient's assessment:				
Improved	13	10	<0·1	P>0·5
Not improved	19	17		

Of the 18 patients receiving control tablets, nine (50 per cent.) said the tablets caused some subjective sensation (apart from the mere taste), whereas the corresponding figure among 22 patients receiving mephenesin was 19 (86 per cent.)—a difference which is significant at the 5 per cent. level. Of these 19 patients who noted some subjective sensation after taking mephenesin, ten did not find any improvement in their symptoms; they said the tablets made them feel "dull" or "giddy". There is thus evidence that mephenesin tablets produce a sensation apart from the effects of suggestion but that this sensation is by no means necessarily associated with relief of symptoms.

The conclusion to be drawn from this trial is that mephenesin, given by mouth in the dose of 1 G. t.d.s., has no clearly defined value in the routine treatment of neurotic states associated with anxiety and tension.

SUMMARY

1. This paper reports a controlled trial of oral mephenesin in neurotic states associated with anxiety and tension. Fifty-nine female patients were studied.

2. The drug was given in the dosage of 1 G. t.d.s. for a week, and the effect assessed clinically.

3. Cases treated with mephenesin showed no significantly greater improvement than cases treated with placebo.

ACKNOWLEDGMENT

My thanks are due to Mr. E. F. Wellington, dispenser at Barrow Hospital, for preparing the placebos and for other assistance in this study.

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OBSERVATIONS ON THE EFFECT OF LARGACTIL IN PSYCHIATRIC ILLNESS

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(Received 20 June, 1954)

LARGACTIL is one of the phenothiazine group of compounds. It is, therefore, related to promethazine (phenergan) and diethazine (diparcol). It is also known as R.P. 4560 and chlorpromazine. It has been used on the Continent in psychiatric cases since 1951, because of the relaxation and calm it produces. It has been on trial at Netherne Hospital since 1953 and 80 patients have received this treatment.

It can be given orally or by intra-muscular injection. Concentrated solutions may cause considerable irritation when given by injection to some patients and in this case the dose should be diluted to 25 mg. in 5 cc. of saline as a minimum. The intra-muscular dosage is from 25–50 mg. 3 or 4 times daily. The oral dose needed is between 1 and 2 times the intra-muscular dosage. There is a wide individual variation in response, the usual oral dosage being between 150 and 200 mg. daily, but some patients can only tolerate 75 mg. while others appear unaffected by 600 mg. daily. In co-operative patients treatment was usually commenced with 25 mg. 3 times daily by mouth and as this as a rule produces little effect, 50 mg. 3 times daily was given the next day, then increasing to 75 mg. 4 times daily if necessary. In the acutely disturbed psychotic, it was found necessary to commence treatment with intra-muscular injections of 25–50 mg. four times daily.

French writers (1) have summarized its properties as "a compound possessing vagolytic, spasmolytic and sedative activity. It is also sympatholytic and adrenolytic, eliminating adrenaline-induced hypertension." They also say it has analgesic activity and enhances the action of other analgesics and hypnotics. An annotation in the *British Medical Journal* (2) pointed out that many of the claims were as yet unsubstantiated. Most Continental reports show that Largactil has been used together with a number of other drugs, so that it has been difficult to assess the precise role of any one of them. The investigation at this hospital was, initially, into the effects of Largactil used entirely by itself.

Largactil produces changes in both the physical and mental states of those who do respond to it. The most marked changes occur after intra-muscular injection. Examination of the nervous system then reveals muscular hypotonia. The pupils, if dilated at the onset of treatment, become reduced in size but reaction to light and accommodation is unaffected. There is often analgesia of an unusual kind. The patients seem indifferent to pain rather than unaware of it. For example, one patient with a recent acute psychosis had severe inflammation around injections in the thigh yet made no spontaneous complaint although when coming to the clinic she walked with both hips and knees flexed, presumably because of reflex spasm. She admitted, when questioned, that in fact her legs were painful, but then at the end of the interview again hobbled back to bed and seemed indifferent to her disability. When this patient was taken off Largactil she then said that she remembered her leg had been very painful and hoped she would not need any more injections. Another example of retained reflex activity is that pinching the skin will produce a brisk pupillary dilatation, although the patient seems indifferent to the pain.

Heat regulation is disturbed. It is this property of Largactil, together with the lowering of basal metabolic rate which follows, which has led to the use of the term "hibernation" for its use in surgery and psychiatry on the Continent (3). In the case of patients in bed in the ward their temperature drops to 96° or 97° F.; we have not tried to produce any further fall. At this temperature they do not behave as if they felt chilled, the skin is warm to the touch and mild sweating is usual.

The cardiovascular system shows the following changes. The blood pressure falls, for example, in one case from 180/110 to 130/80. The fall is most marked in the systolic pressure, so that the pulse pressure is reduced. The fall in blood pressure is most marked in those patients who have a raised and labile blood pressure before treatment and is usually of the degree one would expect with rest in bed and sedation. The pulse rate increases, particularly at the onset of treatment. The facies usually becomes pale. Patients often have a dry mouth but appetite is usually good. Apart from a small increase in volume, no change in urinary excretion has been observed and the blood urea has not altered in any of the cases tested.

The mental state of patients who respond fully to Largactil shows some interesting features.

Such patients are relaxed and if in bed often lie curled on their side with a pale, disinterested facies. Few spontaneous movements are made and they will lie quietly staring at the wall. They are not, however, drowsy and respond to questions. If they do fall asleep in the day, sleep is light and they waken readily. They do not complain nor ask for anything. When food is brought they eat without comment and then lie down again. When they do speak their conversation reveals the disorder of mood and thought characteristic of their illness.

The emotional state is one of indifference and apathy, rather than euphoria, as described by some Continental writers. Questioning too, reveals that the basic mood disturbance continues. For example, a depressed patient who appeared calm and relaxed stated that she still felt depressed, had delusions of having committed some wicked deed and believed she should be punished. The sleep rhythm of depressed patients is also unaffected, early waking still occurs, although they now lie quietly instead of being restless.

There is a marked reduction in irritability, and aggressive impulses become easier to control. In spite of the apparent indifference, affective relationships, likes and dislikes develop. The stream of thought is retarded. Patients tend to answer very briefly but if questioning is persistent it can often be observed that there will be a considerable increase in response and a tendency for the original symptoms to return. For example, a manic patient on Largactil lay quietly in bed. Several questions brought monosyllabic answers but when a persistent effort was made to obtain more response, a brief conversation, in which flight of ideas was evident, ensued. The patient then relapsed into silence again. Delusions persist but the patients appear to be less disturbed by them. Several patients have stated that their hallucinations ceased when given the drug and were able to describe their hallucinatory experiences with insight. This can, of course, occur when the acute phase of a psychosis subsides with or without treatment.

Undesirable responses occur in most patients, particularly at the beginning of treatment but later become less noticeable. Some complain of dizziness, particularly upon sitting or standing up. Three patients received minor cuts or bruises as a result of falling when getting out of bed to go to the toilet. A few have commented on the rapidity of their pulse rate. The dry mouth is an inconvenience and makes talking "sticky". A few have found lethargy and heaviness of the limbs unpleasant sensations. Several patients have complained of dizziness and malaise after a hot bath and I now warn patients to avoid this or any other way in which a large change in external temperature is likely to occur. More severe toxic effects have been observed in 3 cases not having large doses of the drug. In the first case the patient was taking 100 mg. daily in 4 doses and after 3 days complained of malaise and had a temperature of 102. There were no physical signs of infection to account for this and the drug was discontinued for a week. She then appeared quite well physically and a test dose of 50 mg. was given orally. A careful check for the next 4 hours showed little change in her temperature or pulse rate. She ate a good meal in the evening and prepared for bed. Seven hours after taking the drug she vomited and complained of abdominal pain. On examination her temperature was so low that it could no longer be recorded on the usual thermometer, her pulse was barely palpable and respiration shallow and sighing at 16/minute. Her blood pressure could not at first be recorded but gradually appeared at 90/70. Her pupils were contracted and her skin dry and cold. Her abdomen was distended and tense, without visible peristalsis and very little could be heard on auscultation. She vomited again and, as she was resuscitated with blankets and a hot water bottle, gradually recovered. The next day her condition had returned to that prior to taking the drug. Two cases have developed jaundice. This was mild and fluctuating in degree and full recovery occurred in 3 weeks when the drug was discontinued. Tests showed that the jaundice was not of typical obstructive or toxic type.

TABLE I

Clinical Results

No.	Diagnosis	Full relief of symptoms	Much Improvement	Slight Improvement	No Change	Worse
11	Acute Schizophrenic Excitement	—	6	3	2	—
12	Disturbed Deteriorated Schizophrenia	—	4	5	2	1
15	Chronic Schizophrenia	—	2	3	7	3
8	Mania	1	3	3	1	—
14	Endogenous Depression	2	4	3	4	1
14	Disturbed Senile Dementia	—	10	3	1	—
6	Anxiety State	—	3	—	3	—
80		3	32	20	20	5

The effects on psychiatric conditions deserve further discussion.

Acute schizophrenic episodes, it is found, respond most satisfactorily if given large doses from the first. Treatment begins with 50 mg. intramuscularly 4 times daily the first day and 75 mg. 4 times daily the second day if the response is insufficient. Those cases which have shown marked improvement are those with great tension and aggressive impulses—the more destructive and aggressive, the more likely the patient is to respond. Those which failed showed childish over-activity with giggling and "silliness". It should be emphasized that although the patient may be quiet and even apparently co-operative, his psychosis continues beneath his calm. One patient who appeared to be responding very well was observed to have secreted a knife in her bed-clothes and to have spent part of the night making a hole in the wall of the side-room. The effect of Largactil is most marked in the first few days in this group of patients. All have slowly relapsed and this is so constant that we now use the drug only as a temporary measure to enable a full examination to be made and then commence other treatment.

Two groups of chronic schizophrenic illness were treated, one consisted of "quiet" patients, most of whom had been managing in the community and who returned to it after treatment. The "disturbed" group were all long stay patients who had already had most known methods of treatment with no permanent benefit. This disturbed group contained some patients who improved considerably. As with the acute group, it was the tense, aggressive patient who showed the greatest benefit. It has enabled the staff to make considerable progress with their re-socialization—some have been regularly to occupational therapy who previously could be tolerated for brief periods only. Gradual relapse has led to a need for increased dosage in several, but so far none have required more than 400 mg. daily.

The quiet group of chronic schizophrenic patients showed little response. In those cases who did seem to respond, it was likely that other factors played a part—one patient, for example, said she felt much better because she was relieved to find she was not given E.C.T. This group contained 3 patients who became worse. These were all patients with somatic delusions.

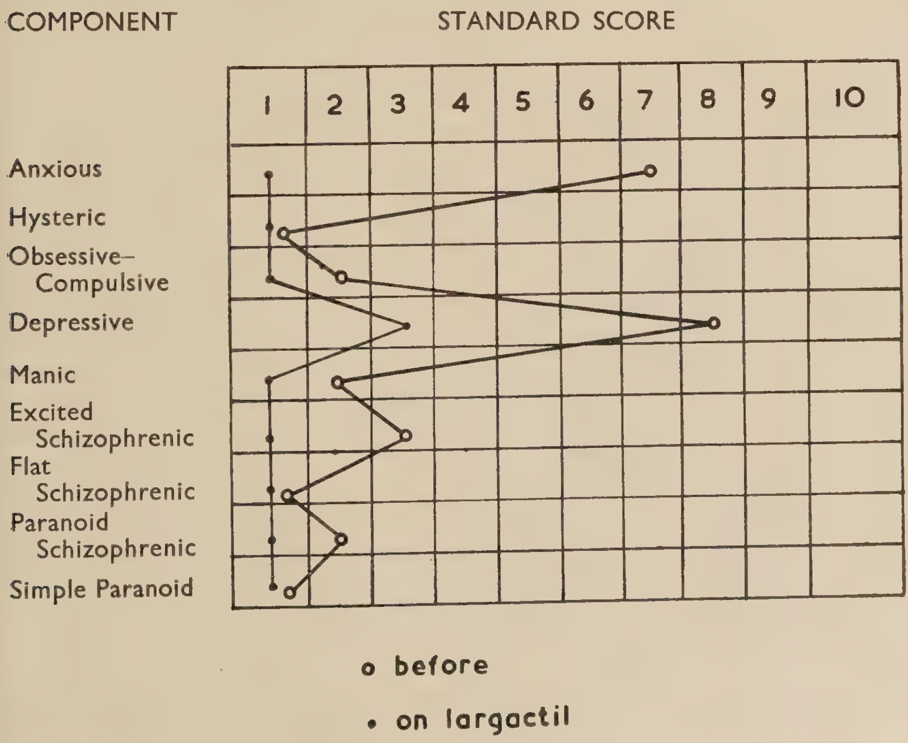
The manic cases have also received large doses from the first day. The response is immediate and is also maintained for as long as the drug is exhibited. It has been found that the most convenient method of administration is to use intra-muscular injections for the first 2 days and then continue the drug by mouth, in roughly 1½ times the intra-muscular dosage. The patient who appeared to make a full recovery had a history of several previous manic episodes. It is probable that recovery would have occurred without the drug, but her period in hospital may have been shortened—her attacks usually lasted 6 months, this one only 3 months.

The cases of endogenous depression have all been in the involutional period and have had varying degrees of agitation. The co-operation of the patient is more readily obtained than in the two previous wildly excited groups of patients and treatment was usually commenced with oral dosage of 25 mg. 4 times daily increasing to 100 mg. 4 times daily if necessary. The usual dosage is 200 mg. daily. As with the manic patients, those who respond maintain their response while on treatment but relapse when the drug is discontinued unless recovery from the depressive phase has occurred. Careful enquiry reveals that the patients obtain good relief from agitation and the somatic symptoms of their depression but the depressive mood itself is but little affected—though the patient may complain less, it is still there. For example, early waking often remains, although the patient will lie quietly and not complain. The content of his thoughts remains depressive, even though he no longer looks so dejected, and delusions are usually unaffected, although the patient may find it easier to ignore them or conceal them. Again a note of warning is necessary, that patients who *look* calm and contented may still be considering suicide.

The group showing the most constant response has been the senile dements with restless behaviour. If restless, the senile dement can present a difficult treatment problem. Sedation may confuse him further. E.C.T., if beneficial, is often only temporarily so and is attended by some risk in the feeble or toxic senile. If ambulant, these restless patients may injure themselves or others; in bed, develop sores and tend to scratch and pick at themselves. It has been found that Largactil is a very useful drug for these patients. Treatment starts with 25 mg. t.d.s. by mouth and rarely is more than 50 mg. t.d.s. required. The patient becomes calm and manageable, eats well and is no longer a nursing problem. Memory loss and disorientation are, of course, unaffected.

The group of anxiety states is too small to justify further comment.

As it became apparent that Largactil was likely to prove a symptomatic method of treatment it was decided that an attempt should be made to assess which symptoms or groups of symptoms responded most satisfactorily. For this purpose the Wittenborn (4) rating scale was used. This scale provides 55 symptoms for assessment. A statistical evaluation has already been made into the significance of these symptoms in each of the common psychiatric disorders. Thus, we have been able to draw a "profile" of our patients to show which components were most prominent in their illness and the response of these to Largactil. For example, the profile of a patient with an agitated depression appeared as follows.



Thirty-four patients were scored on the first occasion after a period of observation and then a second rating made when the patient had been stabilized on the most satisfactory dosage of Largactil.

Table II shows the results of treatment on the basic components.

TABLE II

	No. of patients with no change of score	No. of patients with improvement in score	Total 34
Acute Anxiety	17	17†	
Conversion Hysteric	30	4	
Obsessive Compulsive	21	13†	
Depressive	19	15†	
Manic	12	22†	
Excited Schizophrenic	12	22†	
*Flat Schizophrenic	18	16†	
Paranoid Schizophrenic	21	13†	
Simple Paranoid	26	8†	

* Called hebephrenic in original Wittenborn articles.

† Significantly lower at 1 per cent. level.

All the components except conversion hysteria are significantly lower after treatment with Largactil as assessed by the Dixon-Mood Signs test (5).

A further analysis of each of the 55 symptom scales was prepared and those with a significant reduction are shown in Table III.

TABLE III

1.	Difficulties in sleeping	× ×
2.	Rapidity of change of ideas	× ×
7.	Over-activity	× ×
10.	Lack of interest in food	× ×
11.	Impudence or impoliteness	× ×
12.	Irritability	× ×
13.	Avoidance of people	× ×
14.	Loudness of voice	× ×
16.	Untidiness of appearance	×
18.	Feelings of foreboding	× ×
21.	Difficulties in carrying out plans	× ×
22.	Pessimistic feelings about own case	×
28.	Feelings of anxiety	× ×
34.	Lack of insight into own problems	×
37.	Belligerent behaviour	×
39.	Changes of mood	×
40.	Suicidal tendency	× ×
43.	Difficulties in making decisions	× ×
44.	Distortion of facts in defending opinions	×
47.	Fears of committing an abhorred act	× ×
48.	Irrelevancy or confusion of verbal expression	×
49.	Anxiety over tasks set or new situations	× ×
54.	Exaggerated affective reactions	× ×

Those marked × are significant at 5 per cent. level; those marked × × are significant at the 1 per cent. level.

TABLE IV

The following were not significantly altered:

3. Unjustified sexual beliefs
4. Obsessive thoughts
5. Delusional belief he is evil
6. Gives in easily to others
8. Unaware of others feelings
9. Use made of physical disease symptoms
15. Behaviour disrupted by phobias
17. Engrossed in plans
19. Cannot resist compulsive acts
20. Exaggeration of well being
23. Fears others misunderstand him
24. Patient's thinking clearly delusional
25. No organic basis for complaints
26. Feels systematically persecuted
27. Believes others influence him
29. Organic pathology with emotional basis
30. Concern over orderliness of surroundings
31. Dramatically attention demanding
32. Overt activity is at a minimum
33. Grandiose notions
35. Compulsive acts continuous
36. Great variation in rates of speech
38. Suspects others of homosexuality
41. Failure of affective response
42. No concern over physical handicaps
45. Hallucinations
46. Memory faults
50. Repudiates earlier insights
51. Speech is stilted
52. Shows homosexual interests
53. Lies or steals
55. Characteristically oppositional

The precise site and mode of action of Largactil are as yet unknown. Clinical observations and some special tests do provide sufficient information for speculation. It is clear that the drug does not act on any particular symptom, disease or syndrome, but leads to a reduction in the intensity of symptoms in many conditions. It is unlikely that the site of action is the cerebral cortex. Use of the Wechsler–Bellevue tests does not show evidence of "deterioration" in patients taking the drug who are still able to co-operate. Also cases of severe senile dementia respond well and in typical manner, and here presumably the cortex is severely damaged and cortical function at a minimum. All the evidence at present available suggests that it is subcortical centres which are affected. For example, we have found that the EEG record, when the patient is given intravenous Largactil, shows changes which are similar to those of normal sleep. There is considerable evidence that midbrain centres "activate" the cerebral cortex and Lindsley *et al.* (6) have shown that destruction of the reticular substance of the midbrain causes the EEG record to show a persistent sleep rhythm. Rorschach records taken before and during treatment of a number of patients who have responded favourably show "decreased energy" —as evidenced by decreased productivity and fewer "whole card" responses. The state of quiet indifference which is shown by the patient suggests a marked reduction in basic drives—or loss of "conation" as described by classical psychological theory. The indifference and lack of response to painful stimuli recalls that of patients with the condition known as Akinetic Mutism. The latter condition is now thought to be due to a lesion of the reticular formation in the midbrain.

If it is found that Largactil acts on subcortical midbrain centres responsible for the basic drives which "activate" the cortex, it may then be possible to determine more precisely the part played by the cortex or the relevant subcortical area in mental functions and psychiatric illness.

Summary

The effects of a new drug, Largactil, on some psychiatric symptoms and illnesses are described. The evidence suggests that the drug will prove useful as a symptomatic method of treatment. The most likely uses are discussed and a brief speculation made about the site of action.

Acknowledgments

I wish to acknowledge the help and advice given by Dr. R. K. Freudenberg, who first suggested the use of Largactil. Also, the assistance given by Dr. J. P. S. Robertson with the statistics. We also wish to acknowledge the assistance of May & Baker Ltd., who supplied us with the drug for trial purposes.

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Reviews

Modern Experiments in Telepathy. By S. G. SOAL and F. BATEMAN. Faber & Faber Ltd., London, 1954. Pp. 425. 30*s*.

The phenomena of telepathy remain as baffling as ever, in spite of much devoted work. Prominent as workers are the authors of this book, who give an excellent account of their labours over the past twenty years. Those who want to learn something of the present position cannot do better than consult it.

The book's title is not quite exact, for it also gives an account of some of Soal's work on extra-sensory perception; but the inexactness is not important, for, as Soal shows, the relation between the subjects is close and complex. Most of the results have already been published in technical journals; in the book they are described more comprehensively, and are shown as a series, so that the relations between the parts can be made clear. As a result, the book is readable and coherent, though at times the detail in which the experiments are described makes the reading somewhat laborious. While writing it, the authors must clearly have been in a quandary. With insufficient detail, and too superficial a description, the reader would not have appreciated the thoroughness of the precautions taken; an exhaustive description would have wearied him. In fact, the account given strikes a satisfactory balance.

The reader who wants to form an opinion on the subject must read the book and judge for himself, but a few comments here may not be out of place. In particular, I can say that the statistical methods bear everywhere not only the stamp of competence, which is to be expected of a professional mathematician, but also bear witness to an unusual shrewdness and depth of understanding in the various applications. The matter is worth mention, for Spencer Brown has recently attempted to raise the question whether the results, both of Soal's work and of Rhine's, might not be due to some basic flaw in statistical method. The attempt, however, seems to have come to nothing. Such flaws as Spencer Brown has been able to suggest are mostly capable of direct refutation from the experimental results; in many ways Soal shows both his deep understanding of what is involved and his skill in being able to devise experiments that are independent of such possible flaws. It is the reviewer's opinion that the conclusions drawn by Soal from his results are perfectly justified from the statistical point of view.

What, then, is one to say of Soal's general conclusions? There is no doubt that some of the work done on telepathy and extra-sensory perception can stand comparison with most good scientific work when one considers the care, patience, and ingenuity brought to the work. Soal deserves commendation for the skill he has shown in the experiments and for the patience with which he has sustained an appalling amount of plain drudgery. The evidence he has produced is very strong, strong enough to give ample justification for a belief in telepathy.

Unfortunately, although the long sequences of tests have given results that cannot be ascribed to chance, the *size* of the effect is often small, and one can say that the effect must be due to telepathy only if one can be sure that every possible small ordinary source of bias has been excluded. Exclusion of every conceivable source of small bias is not easy, and those who wish to support the verdict of "not proven" are in no way unreasonable. The position, in fact, is still uncertain. The evidence is very strong—there is no question of that—but one may still doubt whether it is absolutely conclusive. If this view seems contradictory, I can plead only that the facts themselves are still contradictory, so that it does not seem to be yet possible to come to a final decision.

The position seems to me to be strongly reminiscent of that occurring 150 years ago in the phenomena of electricity. At that time only one or two phenomena were known, the relation between them was obscure, and it could be asked contemptuously what connection could rubbed amber possibly have with a frog's twitches? Neither of the phenomena were regularly reproducible, and they doubtless often refused to appear when a special demonstration was staged; (for the occasion would lead to variations in method that were unwittingly fatal to the demonstration, for no one knew what was important). The little that was known about the phenomena made no sense in terms of the science of the day, which recognized only gravitational, mechanical and chemical forces. The phenomena were trivial, and there were plenty of "ordinary" explanations that might have explained them. "Electricity" in those days was not, scientifically, a respectable subject. It may be that these telepathic and other phenomena are similarly just straws that show the movements of an otherwise unobservable atmosphere.

Be that as it may, Soal's book is as good as any written on the subject. It can confidently be recommended. W. Ross Ashby.

General and Social Psychology, By R. H. Thouless. University Tutorial Press Ltd., London. Third Edition, 1951. Pp. 430. Price 17*s.* 6*d.*

"This book is intended for students studying for a degree in psychology"—as such it is quite excellent. It commands one's deep respect.

Much of this third edition has been completely rewritten and account has been taken of "new developments in psychology and new directions of interest". The book is indeed comprehensive.

It is evident that the author has read widely throughout his very big subject; having digested what he has read, assimilated and thought about it, he has presented his knowledge with clarity. The 316 references in the text are blended into a single, clear exposition. The facts and theories of psychology are placed in perspective with an apparent effortlessness which is always the product only of skill. The reader's attention is thus held.

This relatively small volume of well spaced type is packed with knowledge. The author's style is not expansive, he is not verbose and nothing in the book is redundant. This is not a book to be skimmed; it is a text book deserving to be studied, learnt and remembered. C. E. H. Turner.

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A Critique of Psychiatric and Psychological Research on Insulin Treatment in Schizophrenia

After twenty years of research with insulin treatment in schizophrenia the published evidence is inconclusive and contradictory. Wide variations in remission and recovery have been reported but the number of published control studies is meagre. Psychological tests yield no definitive data on prognosis or the effects of treatment. Insulin treatment in schizophrenia continues to pose a major challenge to research.

(Authors' Abstr.)

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Intellectual and Affective Changes in Essential Hypertension

The Rorschach test was administered to 3 diagnostic groups of patients with neurosis, organic brain-damage, and essential hypertension. The subjects were individually matched with respect to color, sex, age, formal education, and I.Q. Intergroup statistical comparisons were made of the mean values on each of the Rorschach variables. The relative frequencies of Rorschach "signs" of organic cerebral damage in the 3 groups were compared using the chi-square technique. The results indicate that the mean scores of the hypertensive group consistently fall between those of the other 2 groups. The Rorschach "signs" of brain damage occur more frequently in the brain-damage than hypertensive group, but there was no significant difference in this respect between the hypertensives and neurotics. An interpretative review of the protocols in the 3 groups indicates a considerable amount of neurotic symptomatology in each group, but confirms the quantitative results which indicated intellectual impairment due to organic brain damage in some of the patients with essential hypertension.

(Author's Abstr.)

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Studies of the Process of Aging: Factors that Influence the Psyche of Elderly Persons

1. The cortical activity of persons over the age of 60 shows a definite change as measured by the EEG. A high percentage have focal dysrhythmias which are primarily found in the left temporal areas. The presence of this focal dysrhythmia alone does not seem to impair psychological function, rather there is questionable evidence that it is associated with more flexibility and an increased ability to learn new patterns. In contrast, a diffuse slowing is accompanied by intellectual deterioration.
2. Guilt is not an important psychic determinant in elderly persons and is not the major cause of feelings of depression. Depression is more often related to loss of self-esteem because of feelings of inferiority.
3. A poor relationship between old people and their children is a part of lifelong pattern of neurotic and immature behavior.
4. Psychologically, elderly persons who continue to work beyond the usual age of retirement have a higher intellectual capacity than those who do not.

All of these findings raise many questions which require further thought and investigation before we have achieved a reasonable and useable knowledge of the factors that influence the psyche of elderly persons.

(Author's Abstr.)

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Prefrontal Lobotomy and Transorbital Leucotomy: A Comparative Study of 175 Patients

1. Favorable results with transorbital leucotomy approximate those with lobotomy.
2. Death, undesirable personality changes, and postoperative convulsions were minimal with transorbital leucotomy in contrast with lobotomy.
3. Psychosurgery should be of a type which causes the least cerebral damage.
4. The high rate of psychosurgical failures, the absence of valid prognostic criteria, and the frequency of relapses preclude clear concepts on the specificity of therapeutic effectiveness as well as on the role of the frontal lobes in the psychopathology.
5. Course and pattern of the schizophrenic psychoses seem to be of great prognostic significance.
6. The therapeutic benefits can be dramatic in individual cases but are rather limited on the whole. It seems desirable to narrow the range of applicability still further in order to obtain more satisfactory results.

(Authors' Abstr.)

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Effects of Prefrontal Lobotomy on Patients with Severe Chronic Schizophrenia

The authors' experience that patients with severe schizophrenic symptoms tend to improve whether lobotomized or not confirms the need for control cases in studies of the effects of lobotomy.

In series rigorously matched regarding the general and specific severity of symptoms, they find that the lobotomized patients show symptomatic improvement with a frequency reliably greater than that of the controls. They appear more nearly normal. Anxiety is diminished. Resistive isolation and schizophrenic disorganization appear diminished and paranoid projection is diminished.

The hypothesis is presented that the splitting of the schizophrenic process is the result of a conflict, unresolvable to the patient, reflected, on the psychological side, by anxious preoccupation and, on the neurological side, by an unresolving morbid resonance or eddy of neural activity between cortex and diencephalon, which jams the higher circuits and leaves the control of behavior to lower centers capable only of stereotyped inflexible and defensive adjustments. Prefrontal lobotomy is presumed to benefit the schizophrenic patient by destroying circuits involved in the maintenance of this morbid eddy or resonance and permitting him more effectively to integrate and use what he has left.

(Authors' Abstr.)

Ventromedial Quadrant Coagulation in the Treatment of the Psychoses and Neuroses

In appraising their therapeutic results the authors have used no formal tests. Before operation they attempted to evaluate the anxiety factor and the interpersonal socio-economic disability resulting from anxiety. In their series this evaluation is usually based on long acquaintance with the patient, members of his family, and friends. Most of the patients selected for operation have been previously treated by them with other methods such as the various shock therapies and psychotherapy for periods of 4 to 10 years. Their final decision to operate represents a "court of last resort" procedure. This decision is reached after many lengthy interviews with the patient, his friends, and his family. Within a reasonable time (3 to 6 months) after operation, they again evaluate the anxiety factor and the interpersonal socio-economic improvement. They consider an end result as satisfactory if the patient is relieved of anxiety and if he is able to adjust himself reasonably well in an environment which was, to him, unbearable before the operation.

(Authors' Abstr.)

Metabolic Studies in Mongolism

1. In order to study thyroid and lipid function in mongolism, the levels of serum protein-bound iodine, cholesterol, and the fraction of S_f 12–20 molecules of lipoproteins were studied in a group of 74 mongoloid patients, and these were compared with the findings in normals and with a group of 18 cases diagnosed as "undifferentiated mental deficiency".

2. There was no significant difference in the serum protein-bound iodine levels between mongoloid children and "controls" of the same age.

3. Mentally retarded children, whether the diagnosis is mongolism or undifferentiated mental deficiency, have significantly higher serum cholesterol levels than normal children.

4. The most marked differences between mongoloids, normal, and control children occur in the level of large molecule lipoproteins of the S_f 12–20 class, the mongoloids being highest, the cases of undifferentiated mental deficiency intermediate, and the normals lowest.

(Authors' Abstr.)

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Chronic Anxiety Symptomatology, Experimental Stress, and HCl Secretion

The evidence that increased HCl secretion occurs during sustained anxiety is contradictory to the unqualified extension of the emergency theory of emotions to chronic emotions. Results of studies with dogs and monkeys indicate that this increased HCl secretion is a function of the change from acute-emergency to sustained anxiety. The problem of the present experiment was to test this conclusion in humans and to obtain further empirical data of HCl secretion and anxiety in humans.

The procedure consisted of (*a*) comparing the fasting gastric acidity levels of seven subjects presenting chronic anxiety symptoms and of a group of seven subjects not presenting such symptoms; and (*b*) comparing the fasting HCl secretory response of these two groups when subjected to one experimental anxiety-evoking situation based upon pain and pain anticipation stimulation and another consisting only of pain anticipation stimulation.

Because of methodological limitations, the desired differential pretest anxiety in the two groups was not obtained. Therefore the nature of HCl secretion during acute-emergency anxiety could not be studied.

The gastric acidity of the original "chronic anxiety" group was greater than that of the control group, but this difference was of only suggestive reliability. When one subject was eliminated from each of these groups on specified grounds in order to make the groups more homogeneous in anxiety, the gastric acidity of the "chronic anxiety" group was significantly greater than that of the control group. When pain and pain-anticipation stimulation and response interacts with the sustained pretest anxiety, there is a significant increase in HCl secretion.

Both these findings are consistent with previous studies of sustained anxiety and HCl secretion. The accumulated evidence (*a*) reveals the invalidity of the unqualified extension of the emergency theory to the chronic emotions involved in psychosomatic disorders and (*b*) reinforces the belief that the role of chronic anxiety in peptic ulcer etiology merits detailed investigation.

(Authors' Abstr.)

Impairment of Mental Function During Electric Convulsive Therapy

The scores of a word-naming test decreased significantly after five or more electric shock treatments.

Recovery took place within one week following treatment, and the word scores continued to increase during the six weeks of observation after the termination of electric convulsive therapy.

A comparable control group of patients showed no decrease but, rather, a moderate increase in word scores on repetition of the test over a three-week period.

A petit mal or partial convulsion did not impair the word scores.

The decrease in word scores is interpreted in terms of temporary inaccessibility of the word-naming faculty during shock treatment.

(Author's Abstr.)

APRIL

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Liver Function and Other Blood Chemistry Tests in Multiple Sclerosis

Fifty-eight nonjaundiced patients with multiple sclerosis were tested with a group of 27 tests for evidence of hepatic dysfunction.

Tests which have been reported to have a significant statistical association with liver cell damage namely, the albumin-globulin ratio, cephalin flocculation, thymol turbidity, and sulfobromophthalein retention tests, and those showing a less degree of correlation, namely highly elevated serum bilirubin and slightly elevated alkaline phosphatase, did not occur in statistically significant numbers in the authors' group of 58 patients. Furthermore, the joint occurrence of abnormalities in these particular tests was also not of statistically significant magnitude.

Total and esterified cholesterol levels, which are said to be depressed below accepted normal standards in instances of liver cell damage, were elevated above the upper limits of normal ranges in a statistically significant number of the authors' patients. The ratio of total to esterified cholesterol was normal in all patients. None of the patients, including those with high cholesterol levels, had jaundice or other clinical disorders associated with high serum cholesterol values.

Abnormalities of total cholesterol, cholesterol esters, lipid phosphorus, serum esterase, inorganic phosphorus, true globulin, Howe albumin, and zinc sulfate turbidity tests occurred with statistically significant frequency in the group of 58 patients studied. These abnormalities are not considered to be related to hepatic function.

(Authors' Abstr.)

Poliomyelitis. The Cerebral Hemispheres

The cerebral hemispheres in 75 cases of bulbar poliomyelitis were studied. Of these cases, 56 were acute and clinically showed no respiratory difficulties, while 19 were subacute and clinically had marked hypoxia prior to death.

Meningeal involvement was extremely common and was observed in 85 per cent. of the authors' cases, all cortical areas being implicated in at least some of the cases. This meningeal involvement was invariably mild and bore little correlation to the inflammatory or neuronal changes within the underlying brain tissue.

In the 56 acute cases, extensive nerve cell damage was observed in 42, or 75 per cent. These neuronal changes were strikingly localized to the large and giant pyramidal cells of Layer 5 and the medium pyramidal cells of Layer 3 of the motor cortex.

The 19 subacute (hypoxic) cases showed neuronal damage in 15, or 79 per cent. The nerve cell damage was more widespread, implicating almost all cortical areas in at least some of the cases. It was felt that the neuronal damage in cortical areas outside the motor cortex in these cases was probably due to hypoxia rather than the disease itself.

A survey of the pathologic changes throughout the nervous system in 10 unselected cases revealed a most consistent and uniform involvement in all areas exclusive of the basal ganglia, suggesting some uniform method of spread of the infection, such as the vascular system.

(Authors' Abstr.)

Poliomyelitis. The Cerebellum

The cerebellum was studied in 75 cases of bulbar poliomyelitis.

It is apparent that the cerebellum is frequently implicated in poliomyelitis, even though clinical manifestations of such involvement are uncommon.

Of the 75 cases studied, 77 per cent. showed at least a minimal amount of inflammatory and/or neuronal change in some areas of the cerebellum.

Inflammatory changes within the meninges were observed in 40 per cent. of the cases and were most frequently encountered over the vermis.

Neuronal changes occurred within all nuclear groups of the cerebellum but were most frequent and severest within the dentate nucleus and the Purkinje layer of the vermis.

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Histopathological Changes in the Brain in Schizophrenia

1. The technological and interpretative precautions which must be exercised in investigations concerning histopathological changes in the brain in schizophrenia are discussed.
2. The literature dealing with such changes in the neurons, glial elements, lipid components, and vascular and perivascular tissues is reviewed. A special section described and comments upon the work of Papez and Papez and Bateman.
3. The findings described are discussed in relation to the design of the investigative procedures used, the precautions necessary for interpreting such findings, and the implications which can be drawn from the contradictory and inconclusive results of 50 years of investigation on the histopathological level.
4. It is suggested that for those who reject the "functional" classification of schizophrenia, the very lack of definitive results from the histopathological approach dictates a new attack on the problem of the etiology of schizophrenia from the level of metabolic dysfunctions in the brain.

(Author's Abstr.)

Laminar Cortical Blocking and its Relation to Episodic Aggressive Outbursts

Experimental studies of the EEG during sleep reveal two types of abnormal EEG responses to auditory stimulation: one, found in patients with organic brain damage, is confined to the side and the site of the lesion; the other, found in some persons with episodic aggressive behavior, is confined to the association cortex of posterior parts of the hemispheres.

The second type of response is characterized by positive bursts that replace the normally occurring biphasic bursts. These evoked bursts are identical with the spontaneously occurring "positive 6- and 14-per-second spikes" observed by Gibbs and Gibbs.

Results obtained by experimental methods showed that positive bursts similar to those seen in the human are reproducible in the animal cortex by blocking of activity of the cortex by topical application of depressant drugs. Positive bursts are also seen during the recovery cycle of "spreading depression" of Lẽao and in general conditions of depression of cortical activity, like deep anesthesia, low blood pressure, and anoxia.

It is inferred that positive bursts in the human EEG. evoked or occurring spontaneously during sleep, are sleep spindles whose negative phase has been reduced or abolished. This may be due to blocking of activity in the superficial layers of the association cortex in the posterior temporo-parieto-occipital region. The high incidence of positive bursts in the younger age bracket suggests that delayed maturation of this region may play a role in the production of the electrical abnormalities and clinical manifestations.

The hypotheses that clinical manifestations (rage, assaultiveness, and accompanying autonomic changes) are release phenomena due to transient laminar blocking of inhibitory mechanisms in the superficial layers of the association cortex is discussed.

(Author's Abstr.)

Ansotomy in Paralysis Agitans

A stereotaxic method for localizing and producing lesions of the ansa lenticularis (ansotomy) has been developed using the foramen of Monro and the anterior commissure as reference points.

Ansotomy is able to reduce and, in some instances, almost completely to eliminate the Parkinsonian tremor on the opposite side. These results could be obtained with preservation of volitional movements or without increase of muscle tone or disturbance of sensation. The ability to perform alternate movements, e.g. flexorextensor movements of the fingers, may even be increased and rigidity sometimes diminished.

The electropallidogram failed to show a relationship of its rhythm to that of the tremor or abnormalities indicative of gross pathologic changes.

Based upon these experiences and upon animal experiments (combination of tegmental stimulation and mesencephalic lesions), a working hypotheses regarding the mechanism of the Parkinsonian tremor is outlined. It is assumed that the static tremor is due to a release of the reflex arcs serving static innervation and synapsing in the rhombencephalic and mesencephalic reticulate substance from inhibitory influences that originate chiefly, but not exclusively, in the substantia nigra.

The part of pallidofugal impulses conducted by the ansa lenticularis probably carries facilitating impulses to the tremor-genetic area in the tegmentum. The role of other pallidofugal fibers is being studied.

(Authors' Abstr.)

Isoniazid Treatment of Psychiatric Patients

Of 65 psychiatric patients treated with isoniazid, only 8 showed any improvement that seemed to be definitely related to the drug or its suggestive effect. The effect of isoniazid on the personality is varied and unpredictable, but in general it appears to be that of a stimulant in smaller doses and of a neurotoxin in larger doses.

Isoniazid is of very limited, if any, value in the treatment of psychiatric patients. It occasionally seems to help overcome fatigue, mental sluggishness, or depression associated with any of the various reaction types.

(Author's Abstr.)

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Autonomic Functions of the Diencephalon

In summary, then, it can be said that the hypothalamus acts as a nerve structure of highly integrative character. Mainly, it seems to activate and organize global activities of the organism which subserve two main purposes. First, there are the mechanisms subserving the purpose of providing the necessary background for externally directed action and reaction; these are the ergotrope activities, mediated in the periphery mainly by the sympathetic nervous system. The second group of mechanisms subserve the purpose of counteracting exhaustion and overstrain and of maintaining the homeostasis of the organism; these are the trophotrope activities and are mediated in the periphery, mainly by the parasympathetic nervous system. Neither activity is purely autonomic in a strict sense, because there is some degree of somato-autonomic integration in these global performances. Each activity is represented in a different area of the basal diencephalon. The ergotrope area covers roughly the posterior medial hypothalamus and shows a pattern of collective representation of ergotrope activities. The ergotrope or "dynamogenous" zone of the hypothalamus is, therefore, functionally homogeneous. Not so the trophotrope zone, which covers an area comprising the septum, the preoptic area, the lateral hypothalamus, and part of the basal medial thalamus. There some topical organization can be seen, with the exception of the lateral preoptic and anterior lateral hypothalamic area, where a pattern of collective representation of trophotrope mechanism is also encountered.

The main characteristic of the functional organization of the hypothalamus is, therefore, quite different from that of the cortex, where the somatotopic type of representation is dominant. In the hypothalamus another principle of organization is realized; there is collective representation of various organotropic effects into global mechanisms subserving common purposes. This integration of various effectors, autonomic and somatic, into patterns of action, each subserving a definite type of performance, seems to be the main characteristic of the functional organization of the hypothalamus.

(Author's Abstr.)

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Circulatory Conditions in Electroshock Therapy with and without a Muscle Relaxant

With use of a mechanoelectronic transducer manometer, the intra-arterial pressure was recorded in electroshock therapy with and without succinylcholine iodide as a muscle relaxant. The venous pressure was measured with an aneroid manometer, and the heart rhythm was also recorded.

The arterial blood pressure is found to rise during the electroshock. When the muscular spasms and the asphyxia are eliminated with the administration of succinylcholine and oxygen, a slower and more even rise is noted; the difference between the maximums with the respective methods is almost significant ($P<0\cdot05$). The pulse pressure, which undergoes considerable variations with the usual technique, is found to be practically normal when a muscle relaxant is given.

An appreciable rise in the venous pressure takes place in conjunction with unmodified electroshock therapy, whereas only an extremely slight rise is noted under the influence of a muscle relaxant and oxygen. The difference is significant ($P<0\cdot01$).

In ordinary electroshock therapy the heart rate is found to be irregular and greatly increased. Muscular relaxation produced by succinylcholine is noted to result in a slower and more even rate. The difference between the increases in the heart rate with and without succinylcholine, respectively, is highly significant ($P<0\cdot001$).

It is concluded that with the use of a muscle relaxant and oxygen it is possible to reduce significantly the strain on the circulatory organs caused by electroshock treatment.

(Authors' Abstr.)

Further Experiences in Use of Thiamylal with Electroshock

Seventy-seven patients have received 1,007 electroshocks in conjunction with thiamylal.

One fatality is reported in which the patient had physical complications severe enough in themselves to cause death.

Electroshock in conjunction with thiamylal is safe, when properly administered, for patients with bony lesions. It is safer than standard electroshock for those with cardiovascular disorders and useful for patients with anxiety regarding the treatment.

(Author's Abstr.)

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Mechanisms of Voluntary Movement

In conclusion, the precentral gyrus can be employed in the performance of skilled voluntary acts even when it has been cut off from surrounding transcortical connexions.

During voluntary dexterous movement of the right hand the resting rhythm of brain waves disappears in the arm area of the pre- and post-central gyri but not in other parts of the Rolandic strip and not on the cortex anterior and posterior to the arm area. It disappears also when the command is given to prepare for movement of the hand. These electrographic observations are consistent with the belief that a subcortico-cortical stream of nerve impulses is directed toward that portion of the precentral gyrus during its employment in willed action.

Many of the final integrative processes that are prerequisite to planned voluntary action must take place in a central position within the brain, in what may be called the centrencephalic system.

The peripheral or efferent connexions of the different portions of the precentral gyrus are arranged in an invariable sequence from one end of the Rolandic strip to the other. These corticofugal connexions are of two kinds: (*a*) to the bulbar and spinal anterior horn areas, and (*b*) to subcortical motor mechanisms, of vocalization, swallowing, breathing, conjugate deviation of eyes, etc. Dexterous, voluntary movements of fingers and toes can only be carried out through the former connexions (*a*).

When the precentral gyrus has been removed, during early infancy when it seems likely that the precentral gyrus is not used, voluntary action is still possible. Under these conditions, dexterous employment of fingers and toes is not possible but skilful use of the subcortical motor mechanisms of swallowing, vocalization, looking, etc., is still possible and gross movement of the extremities as well.

It seems likely that there may be an alternative pathway for directional voluntary impulses. When the motor cortex is not available it would seem that the subcortical motor mechanisms and, to a limited extent, the bulbo-spinal anterior horn centres are controlled by streams of impulses originating in the centrencephalic system without making a detour to the precentral gyrus.

It must remain a matter of speculation as to what use may be made of the direct, extra-cortical pathway of voluntary control, under normal conditions of adult life.

(Author's Abstr.)

An Experimental Critique of the Effects of Anterior Cingulate Ablations in Monkey

1. Twenty monkeys, 12 with lesions of the anterior cingulate gyrus, were used to study the effects of bilateral anterior cingulectomy.

2. Behavioural observations consisted of testing the performance of the animals on the delayed reaction problem, a visual discrimination problem, their reaction to a "frustrating" situation, and their social behaviour. Only with respect to the reaction to "frustration" was any change in behaviour induced by the cingulectomy. Shortened duration of avoidance behaviour resulted from ablation of the anterior cingulate cortex. Although similar changes follow other frontal lesions, these are accompanied by additional impairment—viz. of performance of the delayed reaction type of problem. Thus, medial frontal and cingulate resections have been shown to shorten selectively the duration of avoidance.

3. Anatomical observations with respect to the projection of the anterior thalamic nuclei are of interest. The more posterior the ablation of the cingulate gyrus extends, the more degeneration is found in the n. anterior ventralis. Resection restricted to the anterior portion of the cingulate gyrus results in degeneration limited to a strip at the junction of the n. anterior ventralis and the n. anterior medialis. Invasion of the medial frontal cortex anterior to the corpus callosum is associated with massive degeneration of the n. anterior medialis. The most ventral portions of this nucleus and the n. parataenialis degenerate when the subcallosal cortex is involved. These observations establish the fact that the projection of the anterior nuclei terminate in an orderly manner in the cingulate and medial frontal cortex. An axis through the anterior thalamic nuclei extending from the dorsolateral to the ventromedial positions projects to the cortex along a postero-antero-ventral arc paralleling the corpus callosum above and bending around its genu. In addition, the evidence suggests that the more medial portions of the nucleus project to the more hilar portions of the cortex. No differentiation of the projection of the antero-posterior axis of the nucleus is apparent.

(Authors' Abstr.)

Delusional Reduplication of Parts of the Body

Four cases are described in which there were reduplicative delusions of the existence of extra parts of the body. One patient with a left hemiplegia confabulated having an extra left hand; another with a left hemiparesis and a fracture of the right leg stated that he had four legs; a man with a cerebellar astrocytoma and meningitis confabulated having multiple heads and a patient with a severe head injury who previously had an eye enucleated expressed the delusion that he had several eyes. In all cases the pathology was of rapid onset and associated with a diffusely slow-wave EEG record.

In each case reduplication of body parts was associated with other forms of reduplication for time, place or person. Accordingly, the phenomenon is considered as being but one manifestation of a general pattern of reduplicative delusions.

Reasons are given why such delusions cannot be explained either as a specific defect resulting from the destruction of any particular area of the brain, as a perceptual disturbance, or in terms of an alteration in "body scheme" in the sense that the body scheme is a three-dimensional image of the body with a representation in the parietal lobe.

The delusion of reduplication occurs under the same conditions of altered brain function as do anosognosia, disorientation for place and time, and "paraphasia". As with these phenomena, the patterns of reduplication may be used as symbolic mechanisms to express some personal motivation, particularly the denial of illness.

(Authors' Abstr.)

A Hypothesis Regarding the Brain Modifications Underlying Memory

It is suggested that in certain cortical regions cytoplasmic transmission supplements neurone surface transmission, and that the memory modification consists in the ordering through many cells of previously disordered or less ordered cytoplasmic protein chains or fibrils, in such a manner that the region thereafter responds more easily to repetition of the same stimulus. These extended orderings constitute pulsating structures which are reinforced by the activity which they facilitate. This hypothesis helps to account for properties which appear not to depend solely on the cyto-architecture of neuronic surfaces, such as synchronous mass action, pattern effects, and the fact that memory traces are normally simpler than the activity which they record.

(Author's Abstr.)

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Photogenic Epilepsy: Self-Precipitated Attacks

Seven examples of photic epilepsy in which attacks were precipitated by the subject, have been described in detail.

The common feature was the precipitation of attacks by rhythmical interruption of sunlight falling on the patient's eyes. The flicker may be produced by movement of the fingers or the hand in front of the eyes, or by blinking.

The attacks were usually slight and of brief duration, with varying degrees of impairment of consciousness. If flicker was repeated for a lengthy period jactitation and major attacks might occur. In some of the patients major attacks occurred independently, but these were few.

Electroencephalograms of self-induced attacks showed varying forms of spike and slow wave discharges of high voltage, usually irregular and usually of brief duration.

Encouragement of voluntary inhibition of the provoking movement proved to be the best method of treatment.

(Author's Abstr.)

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Effects of Extraneous Poisons on the Nervous System. II. The Alcohols

The effects of alcohol on the nervous system may be either acute or chronic. The acute effects occur in the form of congestion (at times with petechial hemorrhages) and edema and are usually reversible with restoration of the normal state. After repeated severe episodes of intoxication the abnormal physiological processes, reinforced by malnutrition and deficiency states, are translated into cellular and architectural changes which are accompanied with more or less characteristic symptom-complexes. Thus delirium tremens is found to be associated with a widespread pyknosis and acute swelling of the various orders of pyramidal cells of the cortical laminae. Korsakoff's psychosis and psychotic manifestations incident to post-alcoholic pellagra are found to be accompanied by a precocious and almost universal deposit of lipoid material in the nerve cells of the brain and spinal cord. A frontal lobe syndrome, reminiscent of general paresis (alcoholic pseudoparesis) results from atrophy of the dorsolateral, frontal, and central cortex. A hemorrhagic encephalopathy of the gray nuclear masses adjacent to the third and fourth ventricles and intervening cerebral aqueduct gives rise to extraocular palsies usually associated with impairment of consciousness and disordered mentation. The peculiar syndrome known as Marchiafava-Bignami's disease, with degeneration of the midportion of the commissural pathways, notably the corpus callosum, much less often of symmetrical foci in the frontal cerebral centrum and middle cerebellar peduncles, results from an excessive indulgence in crude Italian red wine in the presence of malnutrition. The sequence of chronic alcoholism and deficiency states is best seen, however, in case of the more common peripheral neuropathy which in some individuals develops quickly after use of muscatel wine even in moderation.

The indirect effects of chronic indulgence in alcohol is typified by degeneration of the posterior and lateral columns of the spinal cord (posterolateral sclerosis) consequent to atrophic gastritis and anemia. Those effects resulting from alcoholic cirrhosis and uremia are to be classed as toxic, for no specific structural changes in the brain are necessarily to be found.

(Authors' Abstr.)

The Problem of Cerebral Atrophy in the Adult

The history and literature dealing with cerebral atrophy has been briefly reviewed. The recent study of Neumann and Cohn dealing with the clinical and histological characteristics of Alzheimer's disease as seen in a large mental hospital, has been summarized in more detail. In light of these studies it seems logical to conclude that Alzheimer's disease is a definite clinical entity with specific histopathological findings in the brain, and although more common in the older persons, it may be found over a wide age span and is not essentially a presenile or senile manifestation. These conclusions in the literature were apparently based on studies largely from mental hospitals.

The findings in the series of 200 cases of cerebral atrophy, 100 from the records of a general hospital and 100 from the practice of neurology, are contrasted with the findings from mental institutions. In this series 40 per cent of the 55 general hospital patients from 60 to 90 years had mental deterioration or psychosis. Only 7 per cent of 100 patients 25 to 55 years of age seen in neurological practice were deteriorated. Convulsion was the most common single symptom in the entire 200 patients. Various neurological abnormalities, which often resembled other brain diseases, were very common. Although cerebral atrophy is associated with abnormal physical and laboratory findings, air studies are the only means of accurate diagnosis. A problem is presented: Are these apparently idiopathic cerebral atrophies found in the young and middle adult age group related to Alzheimer's disease or are they a separate disease entity or entities? The present writers are of the opinion that they represent a different disease process. No doubt long range studies will be necessary to answer this question.

(Authors' Abstr.)

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Cobra Venom Therapy in the Neuroses

1. Cobra venom appears to be an effective therapeutic agent in some neurotic states and should be more thoroughly studied.

2. Cobra venom is a safe therapeutic agent if properly used and its effect appears to be prolonged.

3. The improved concentrated form of cobra venom is preferred for treatment as it gives less side reactions.

(Author's Abstr.)

Analeptic Action of Oral Metrazol in Geriatric Practice

Of the 39 senile patients on whom Metrazol was tried, 30 or 77 per cent were improved. Of these, 11 or 28 per cent were markedly improved while 19 or 49 per cent showed minor improvement. However, even of these cases 7 or 18 per cent were so much improved that they could be transferred to a home for the aged. The other 9 or 23 per cent showed no change in their status.

As a result of the authors' experience all patients admitted to their male geriatric building are now routinely given one week's adjustment period, and then started on Metrazol in increasing dosages until 3 tablets four times a day are given. If no result is obtained at the expiration of 30 days, the patient offers little chance of improvement and the drug is discontinued.

From the described cases they feel that Metrazol has a definite place in the therapy of geriatric and psychiatric cases and should be prescribed for all patients admitted to the geriatric service in the described dosage for at least four weeks. If possible, the drug should be given early to arteriosclerotic and senile patients in an attempt to prevent, or at least delay the onset of a psychosis or a mental confusion necessitation hospitalization.

(Authors' Abstr.)

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Studies on EEG and Sex Function Orgasm

EEG studies were performed during orgasm obtained by self-stimulation. These records showed the following features, common in all the subjects investigated.

1st phase. There is a sudden increase of rapid activity, particularly emanating from the temporal areas. Simultaneously, with the increase in fast activity, there is a sudden rise of muscular action potentials, superimposed in all the cortical areas recorded.

2nd phase. Simultaneously with the ejaculation in male and the corresponding effects of orgasm in the female subjects, there is a generalized slowing of the electrical activity, with three per second generalized activity, and alternating muscular discharges which persist and are followed by a 3rd phase, in which a depression of the electrical activity with alternating rhythmic, clonic muscular discharges, is recorded.

The EEG studies demonstrate the participation of the entire nervous system, specially the autonomic and cortico-diencephalic portions, and the physiological response of an orgasm.

The cortico-diencephalic interrelationship is stressed and the similarity of events in both orgasm and epileptic convulsion is emphasized.

(Authors' Abstr.)

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The Effect of Bulbocapnine upon the Spontaneous Electric Activity of the Brain and its Reactivity to Afferent Stimuli

1. In catalepsy producing doses bulbocapnine has a slight depressive effect upon the electric activity of the cerebrum, that may be detected in the prosencephalon, diencephalon and mesencephalon. It affects chiefly the fast activity. Only occasionally slow waves or transitory excitatory states were seen with the doses used.
2. In the cataleptic state the reactivity of the cortex and various subcortical areas (hypothalamus, reticulate substance of the midbrain, cerebellar cortex) to afferent impulses is preserved, or even increased.
3. Simultaneous recordings from cortex and various subcortical areas reveal rather variable differences in the degree in which these regions may be affected, indicating that some degree of independence of the functional states of these regions may exist.

(Authors' Abstr.)

The Sedation Threshold. A Method for Estimating Tension in Psychiatric Patients

1. The main aim of this study was to develop a method for objective quantitative estimation of degree of tension in psychiatric patients.
2. Development of the procedure was based on the common clinical observation that sedation tolerance and degree of tension are closely correlated. Sodium amytal was administered intravenously at a constant rate while the EEG was recorded. The discovery of a definite point of inflection in curves of EEG amplitude plotted against amount of sedative provided an objective threshold value. The EEG threshold point usually coincided with onset of slurred speech.
3. This EEG sedation threshold was found to be highly correlated with clinical ratings of degree of tension in 69 psychiatric patients (including 54 psychoneurotics), who were not psychotic at time of testing. The correlation was low in a group of 11 psychotic schizophrenics.
4. Frequency analyzer studies in 10 tests confirmed the quantitative EEG aspects of the sedation threshold method. They also showed that with progressive sedation, the amplitudes of the frequencies in the frontal EEG were increased in an orderly progression from the faster to the slower frequencies.
5. It was concluded that the sedation threshold method seems to hold exceptional promise as an objective psychiatric test, provided that it is properly developed. The implications of the results for understanding the neurophysiological mechanisms underlying pathological tension were discussed.

(Author's Abstr.)

The Electroencephalogram of Normal Aged Adults

Electroencephalograms were taken on a group of 150 normal males ranging from 65 to 94 years of age. These consisted of routine waking monopolar and bipolar tracings, including 3 minutes of hyperventilation. The following results were obtained:

1. Using a scheme devised by Gibbs and his associates for the classification of dominant frequency, it was found that elderly males have a much higher incidence of "slightly slow" (S_1) electroencephalograms than do young and middle-aged adults.

2. Measurements of occipital alpha frequency reveal a shift in the distribution of individual scores to the slow side. When compared with young adults, there is a decrease in the number of cases with 11 to 12/sec. activity and an increase in cases with 7 to 8/sec. activity.

3. Measurements of per cent-time alpha suggest a slight reduction of alpha activity in old age, but the results here are inconclusive.

4. Frequencies above the alpha range (beta waves) were found in approximately half of the subjects, and were the dominant frequency in about 12 per cent. In this respect the senile EEG is similar to that of middle age.

5. Frequencies below the alpha range (delta waves) appear in only 13 per cent of the entire sample, with a greater incidence in people over 80 years of age (17 per cent) as compared with those under 80 years (9 per cent).

6. Response to hyperventilation was either absent or small, which is similar to the findings in middle age. The results are not conclusive, however, because of the possibility of inadequate gas exchange.

A possible relationship has been proposed between frequency alterations in the aged EEG and cerebral metabolic factors and mental deterioration.

(Author's Abstr.)

The Electroencephalogram in the Senile Psychoses

Analysis was made of the EEGs of 50 mentally normal seniles and 104 patients suffering from senile psychosis. The following are the results and conclusions:

1. Twenty-four per cent of the normal group possessed abnormal EEGs. In normal old persons slow activity does not appear to be a characteristic EEG abnormality, in fact there is a tendency for paroxysmal fast activity to be prominent. Old age is however associated with a significant decrease in alpha frequency, amplitude and per cent time.

2. Fifty-four per cent of the psychotic seniles possessed abnormal EEGs. The characteristic abnormality of the senile psychoses is diffuse delta and theta rhythm or diffuse theta rhythm. There is an association between incidence of non-normal EEGs and degree of senile dementia, the likelihood of a normal EEG being lessened with increased dementia.

3. A significant relationship was found between alpha index and degree of senile dementia: alpha index decreases with increased dementia.

4. The finding that the incidence of abnormal EEGs among depressed and paranoid seniles was not significantly different from that in other forms of senile psychosis, was adduced as favouring a common aetiology for these conditions.

5. Amongst 10 preseniles, only 1 possessed an abnormal EEG and 2 were questionable. Study of larger numbers is indicated before any definite conclusions can be drawn from this finding.

(Authors' Abstr.)

Electroencephalographic Changes in Procainization of the Frontal Lobes

1. Procaine injected into the fronto-thalamic fibers produces transitory slowing in the EEG in the majority of cases.

2. Almost complete electrical suppression was observed following 9 of the Procaine injections in which Procaine escaped into the subarachnoid or ventricular system.

3. Paroxysmal cerebral dysrhythmia was observed in the recovery phase following 9 of the Procaine injections.

4. Isotonic saline produced little change in electrical activity.

(Authors' Abstr.)

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Personality Changes Following Transorbital Lobotomy

This study was designed to investigate the personality changes effected by a particular type of psychosurgery, transorbital lobotomy. The experimental or operative group was composed of eight hospitalized psychotic patients. From the parent hospital population, eight control subjects were selected on the basis of their close resemblance to the individual members of the experimental group in regard to seven criteria by which they were matched. The Rorschach test was administered to both groups one month prior to, and one month following, the date on which the experimental group received the operation. During the interim between pre- and post-testing, every effort was made to control environmental rariables; members of each matched pair were treated alike, except that the controls did not veceive the operation. However, the controls did receive electroshock treatments comparable in number to those given the experimental Ss on the day of operation.

Four Rorschach factors significantly differentiated between the control and experimental groups. There was a significant decrease of m% and FK% and a significant increase in W% Reaction Time in the experimental group following the operation. From these data it can be inferred that transorbital lobotomy results in a lessening of inner tension, a lessening of introspective self-awareness and insight, and a loss of ardent enthusiasm and active interest. The significant increase in W% is difficult to interpret except as some change in apperception. These findings and their implications should be considered if psychosurgery of this type is planned.

(Authors' Abstr.)

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The Etiology of Mongolism

This paper is based on detailed case histories of 150 mongoloids, taken by the personal interview method, and on personality studies of their mothers. According to the probably leading etiologic factor in each case, the material was divided into three main groups with several subgroups.

Advanced maternal age does not play a dominating role in the material presented here. The "functional" age is more important than the chronological age. Those mongoloids who were born the first children of young mothers out-number the "menopausal babies".

Adolescence in the mother may bear the risk of mongolism in her first child, especially in those very young women who had a late menarche or menstrual irregularities before marriage. In these young mothers, as well as in some older ones (see Cases 10 and 14 of this paper), the mongoloid does not mark the end, but the beginning or regaining of fertility.

Attention should be paid to ovarian cysts and obliterated tubes. These local disorders were obviously responsible for the development of a mongoloid in several cases of this material.

A nervous, emotional disposition of the mother appears to be a frequent conditioning factor in mongolism of her offspring. It was found in 66 per cent of the younger mothers in this material. In 24 instances, psychic disorder or severe emotional disturbance in the mother at the time of conception was considered to be the leading etiologic factor.

The experiences of this study, in agreement with generally accepted facts concerning the physiology and pathology of sexual functions, support the old "germinal" hypothesis regarding the etiology of mongolism, which may be formulated as follows.

The mongoloid develops as the result of fertilization of a subnormal ovum, just at the borderline between sterility and fertility. The startling multiplicity of "conditioning factors", which are operating before or at the time of conception, are only different roads leading to the same destination: the ovary. They all cause a temporary or permanent ovarian dysfunction with consecutive production of a subnormal ovum. The fate of the mongoloid is already sealed with the fertilization of a "borderline" ovum.

Whether or not all the pathologic constellations discussed in this paper lead to the development of a mongoloid only under the condition that a hereditary gene is present at the same time, cannot be decided. The evaluation of various "conditioning factors", as presented here, does not pretend to be a final solution of the complex problem of mongolism, but may bring us closer to its understanding. It helps to explain 95 per cent of the cases of mongoloids and to give constructive advice to their unfortunate mothers.

(Authors' Abstr.)

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The Conditioned Reflex in the Chronic Schizophrenic

The results of two experiments, with different patients, experimenters, and conditions, agree in showing (1) greater reactivity of the PGR to the UCS in normals and in chronic schizophrenics who have been through three months of problem solving than in chronic schizophrenics who did not receive the learning treatment; and (2) that normals and treated chronic schizophrenics are more readily conditioned than are untreated chronic schizophrenics.

Since evidence presented in a previous paper indicates that the test patients were in better clinical condition than the controls, and of course the normals may be safely assumed to be so, these results bear out Gantt's positive finding that CR is an indicator of clinical condition.

These results are also in agreement with Pavlov's "pathological inertia" hypothesis of the nature of schizophrenia. The relatively low level of reactivity of the chronic schizophrenic's PGR to UCS and the low conditionability are evidence of the characteristic rigidity or inertia of the schizophrenic. Furthermore, the results of these studies suggest that this inertia occurs on the reflex as well as the cortical level.

In the opinion of the writers the major significance of the results of these conditioning studies lies in the support they lend an hypothesis about cortical functioning in chronic schizophrenia. If a part of chronic schizophrenia is a condition of the cortex approximating functional decortication, then a prolonged period of activity which forces the patient to use his cortex—such as the learning problems used with the test patients here—should to some extent improve the functioning of the cortex. Assuming that the CR is an indicator of the level of this cortical functioning, the present results can be interpreted as verifying this hypothesis.

(Authors' Abstr.)

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Disorders of Neuro-Psychiatric Patients in Perceiving Pictures

Samples from eight categories of neuro-psychiatric patients were shown twelve colored magazine photographs and asked to describe all that they saw in each. Twenty-three variables in their descriptions were defined and counted and the categories were statistically compared in regard to each variable. It was concluded that there are two chief classes of perceptual disorders in this situation, those dependent on general intellectual impairment or inefficiency and those not so dependent but related to bizarre thinking.

(Author's Abstr.)

Judgments of Premorbid Intellectual Functioning in Severely Impaired Psychiatric Patients

In order to study psychologists' estimates of premorbid intelligence based on the Wechsler-Bellevue and the case history, seven psychologists were asked to rate the Wechsler-Bellevue protocols and the case histories of ten severely impaired patients for their premorbid intelligence. The results indicate that, while there is some agreement among judges in the estimates made, there is sufficient disagreement to indicate that this is an area that needs further research if the psychologist is to fulfill more adequately his responsibility in evaluating premorbid intelligence.

(Authors' Abstr.)

A Transposed Factor Analysis of Schizophrenic Performance on the Bender-Gestalt

1. In an attempt better to understand the classification of the schizophrenias and diagnostic features of the Bender-Gestalt Test, the performance of thirty-two male schizophrenics on the Bender-Gestalt was subjected to a transposed factor analysis. Ratings of psychiatric characteristics provided information about individuals with particular types of Bender performance.

2. The factor analysis disclosed a large commonness among the Bender performances of the individuals in this study. Four types of schizophrenics were suggested. They are as follows: (*A*) Chronic Undifferentiated Schizophrenic, (*B*) Disorganized Schizophrenic, (*C*) Conforming and Non-defensive Schizophrenic, and (*D*) Actively Defensive Schizophrenic.

3. No general factor of "schizophrenia" appeared. The results of the study are discussed in relation to previously reported schizophrenic types.

(Author's Abstr.)

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Effects of ACTH on Mental Function

An attempt was made to determine if ACTH regularly produces striking, specific changes in mood and behavior as has been reported by some observers. Special attention was directed toward controlling several factors which have complicated evaluation of previous studies. Among these variables are:

1. The presence of severe or chronic illness.
2. The patient's previous personality patterns.
3. Current environmental stress.
4. Attitudes of the investigators.

A group of 11 young male soldiers only mildly ill with acute hepatitis was chosen for investigation and subdivided into control and treatment groups. The pattern of distribution was kept secret from all observers. Periodic psychiatric observations were made before, during, and after the administration of the drug (or placebo).

Psychiatric observations revealed no gross intellectual, affective, or behavioral changes; controls could not be differentiated from patients getting the drug. A battery of psychologic tests was administered during the base-line period and repeated during the course of the drug administration. The psychologic test results did not demonstrate any sharp distinctions between the two groups, either before or after the initiation of treatment. Over-all level of intelligence, patterns of frustration-aggression, and imaginative responses to projective tests remained largely unchanged for both groups. Such fluctuations in test scores and performance as were observed were minor in nature and occurred with equal frequency in the two groups.

It is concluded that major psychologic changes need not invariably occur with the use of ACTH. It is believed that such changes are probably rare in patients who do not have chronic, severe illness either physical or mental.

Although this is a small sample, the strikingly uniform lack of major psychologic changes suggests that the central pharmacologic action of ACTH on the central nervous system (as shown by EEG evidence) has no specific effect on mood and behavior when administered in the usual clinical dosages. It is further postulated that the variables which this study attempted to minimize are probably among the chief factors responsible for the production of mental changes when they occur.

The advantages of close co-operation between psychiatrists and other medical specialists in the evaluation of therapeutic drugs and problems of rehabilitation are discussed.

(Authors' Abstr.)

Relationship Between Capacity for Abstraction in Schizophrenia and Physiologic Response to Autonomic Drugs

1. The relationship between abstraction capacity and blood pressure response to intramuscular mecholyl was investigated in a group of 20 chronic schizophrenic subjects.

2. Abstraction capacity was measured by ability to interpret proverbs. Three related aspects of the systolic blood pressure reaction to mecholyl were measured—maximum fall, area under resting blood pressure levels, and time for recovery.

3. The results indicate a positive correlation ($p = \cdot 05$) between abstraction capacity and each measure of the blood pressure response following mecholyl.

4. The results confirm previous investigations on a group of acute schizophrenic patients.

5. Results of a series of experiments on schizophrenia from the Boston Psychopathic Hospital research laboratories suggest two polar types of schizophrenia: one with poor abstraction, disorganization of personality, slight response to mecholyl, and poor prognosis; the other with good abstraction, good personality organization, marked response to mecholyl, and relatively good prognosis.

(Authors' Abstr.)

Intravenous Sodium Iodide in the Treatment of Advanced Senile Psychoses and Arterio-sclerotic Cerebrovascular Disease

Sodium iodide in the treatment of advanced senile psychoses and arteriosclerotic cerebrovascular disease resulted in no improvement in this series of 15 patients in the dosages given and in the number of treatments given. The 2 deaths in the authors' series made them hesitate to continue the treatment further by either enlarging the dosage of iodides or extending the number of treatments beyond ten. The fact that no improvement was noted in any of the 15 patients treated makes the authors doubt the efficacy of the use of sodium iodide in advanced senile or arteriosclerotic psychoses.

(Authors' Abstr.)

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The Effect of 1-Isonicotynl 2-Isopropyl Hydrazide (IIH) on the Behavior of Long-term Mental Patients

1. Three groups of 30 female patients each were selected from a ward housing between 115 and 120 female patients. The three groups were matched for behavioral averages according to the L-M Fergus Falls Behavior Rating Scale and for body weight. One group received IIH (Marsilid), another group received identical placebos, and the third group received neither IIH nor placebos. The patients were rated once a week for a 24-week period.

2. The differences between the groups were never great enough to be of practical significance.

3. (*a*) In the behavioral area "attitude toward other patients" the drug group showed itself to be significantly superior to its pre-experimental level. (*b*) The untreated control group showed itself to be worse than it was before the experiment started in regard to psychomotor activity and speech. At certain times, especially in the period after the drug was removed, the drug group showed itself to be significantly worse in terms of psychomotor activity.

4. (*a*) The drug group showed numerous trends in practically all areas of behavior (and weight) superior to the other two groups during the 16 weeks the drug was administered. These trends are of theoretical and statistical significance as they indicate that something must be occurring as a result of the drug, although this "something" is not very much. After the drug was removed, the drug group showed no significant differences from the other two groups. (*b*) The untreated control group showed certain downward trends in most behavioral areas.

5. One must conclude that there is a certain small positive effect of the drug over and above that which could be attributable to either chance or to the effect of increased attention. The trends and changes observed existed only as long as the drug was being administered. One must also conclude that the untreated group showed a worsening of behavior that separates it in a minor way from both the placebo and the drug-treated groups.

6. The ward as a whole now requires less sedation, less EST, and less nursing attention to details of dress and toilet habits than it did before the experiment.

7. "Total Psuh" is far more effective than Iproniazid in the treatment of long-term mentally ill people.

8. Iproniazid used alone is not a "miracle cure" in the sense of bringing about major improvement in the long-term mentally ill which would make for their being better adjusted hospital citizens or for remission of their psychosis. Further research will be necessary to determine whether it is useful as an adjunct to other form of therapies.

(Authors' Abstr.)

Electroencephalographic Studies in Posthypoglycemic Coma

1. Twelve cases of posthypoglycemic coma were studied by the EEG.

2. The comas varied in length from one to 20 hours.

3. In contrast to the routine treatment comas, the EEG in these cases showed persistent abnormality for many days after recovery from the coma.

4. There was a close correlation between the length of the coma, organic confusion, remission of mental symptoms, and the degree of abnormality in the EEG.

5. The EEG did not portend the posthypoglycemic coma.

6. The posthypoglycemic coma was not considered as an indication to terminate insulin treatment.

7. It is postulated that the posthypoglycemic coma is a convulsive phenomenon which leads to an iso-electric condition across the semipermeable membranes of the neurones. The iso-electric condition is felt to be a postictal exhaustion state resulting from an excessive electrical discharge of highly suppressed cells.

8. It is felt that interruption of coma could be brought about by the re-establishment of potentials across the membranes which would again permit cellular exchange of metabolites.

9. The administration of anticonvulsants during insulin therapy might in some instances function as a safeguard against posthypoglycemic coma.

10. Further investigation referable to the possibility of an iso-electric state is contemplated.

(Authors' Abstr.)

DECEMBER

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Neuropsychiatric Patients Reported Cured at St. Bartholomew's Hospital in the Twelfth Century. *Wilmer, H. A., and Scammon, R. E.* 1
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The Long Term Evaluation of Prefrontal Lobotomy in Chronic Psychotics

Forty-six lobotomized subjects were studied by the control method eight and one-half years after surgery.

1. It was found that one-third of the patients developing convulsions had their initial seizure between five and six years postoperatively.

2. Of the 20 operatees showing the greatest degree of improvement 25 per cent reached their peak of adjustment within one year after surgery and 60 per cent within five years, but an additional 40 per cent continued to improve up to eight years postoperatively.

3. A regression in behavior was observed in some cases, apparently independent of age, where a high peak of adjustment had been maintained for a number of years after lobotomy.

4. There was no relationship found between degree of improvement and sex, nor between degree of improvement and the occurrence or absence of convulsions.

5. There was a statistically significant positive correlation between degree of improvement and age at time of operation, and a significant negative correlation between degree of improvement and length of time of institutionalization prior to surgery. These findings were thought to emphasize the importance of psychic tension in the selection of patients for lobotomy since the individuals showing the least degree of improvement were those patients with an early age of onset of psychosis and the patients who had been hospitalized for the longest periods of time. In both instances, preoperative psychic tension would be at a minimum.

6. While only 4 per cent of the control subjects (no surgery) showed marked improvement or complete recovery and 88 per cent of the controls remained the same or became worse, 44 per cent of the matched operatees reached the top adjustment levels and only 8 per cent remained the same or became worse. Subdivision of the two groups into reaction types (schizophrenia and affective psychosis) showed a much greater degree of improvement of the operatees for both diagnostic groupings.

7. There was no statistically significant difference in the mean degree of improvement between the two main diagnostic categories of the operatee group.

8. Within the control group there was found to be a statistically significant difference in degree of improvement favoring the affective psychosis group. While the affective disorder group had showed a certain degree of improvement without treatment, the schizophrenic group had become somewhat worse.

9. There was a statistically significant difference favoring the control group on the Picture Arrangement test of the Wechsler and on the Porteus Mazes. This would suggest a permanent decrease in ability after lobotomy in these particular areas of test performance which are believed to relate to the ability to look ahead planfully and to size up total aspects of social situations.

(Authors' Abstr.)

On the Glucose Tolerance Test and the Effect on the Formed Elements of the Blood of Glucose and Epinephrine in Schizophrenia

1. The observation of Freeman and Elmadjian as well as others concerning the delayed rise of blood sugar during the oral glucose tolerance test in schizophrenia has been found valid statistically for a group of schizophrenics, but not as a uniform response in all schizophrenic individuals.

2. The intravenous glucose tolerance test shows no features distinguishing schizophrenics from normals at the one half, one or two hour points but does show a significant continuing fall in sugar value at three hours in the schizophrenics group.

3. No concomitant failure of eosinopenia or lymphopenia has been found in schizophrenics as compared to normal individuals.

4. The Thorne test of schizophrenics shows no statistically significant defect in response.

5. The observed statistical deviation from the norm in the glucose tolerance of schizophrenics is apparently related to an alteration in the uptake of sugar from the gut. The mechanism underlying this alteration is as yet not clear.

6. It is concluded that the observed alteration in absorption is associated with schizophrenia, but has no direct relation to the process in the sense of either etiologic significance or a necessary consequence of whatever physiologic processes may prove to be concomitant with the psychologic disturbance.

7. It is further concluded that neither glucose nor epinephrine constitutes a sufficient stress for the differentiation of a schizophrenic from a nonschizophrenic population, where the response of formed blood elements are utilized as an index of adrenal responsivity.

(Authors' Abstr.)

FEBRUARY

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Clinical Reactions of Schizophrenics to Sodium Amytal, Pervitin Hydrochloride, Mescaline Sulfate, and D-Lysergic Acid Diethylamide (LSD 25)

1. Sodium amytal, pervitin hydrochloride, and mescaline sulfate were administered independently to each of 55 schizophrenic patients, of whom 25 received LSD 25 in addition. The resultant effects were described and analyzed in terms of normalization (reduction) and intensification (increase) of the pre-existent clinical symptomatology.

2. Each of these drugs produced specific effects in two categories (*a*) direct or basic or primary pharmacologic activity, (*b*) characteristic effects on mental symptomatology which were a more or less direct consequence of the pharmacologic action. In the latter category, amytal may be classified as preponderantly a normalizer of clinical symptomatology; mescaline and LSD 25 as intensifiers; while pervitin tended to produce an unstable state with grossly equal representation or normalization and intensification responses.

3. A subgroup of subjects existed, each of whom showed intensification reactions with each drug that was administered. This and other findings which have been presented indicate that the total effects of drug administration seem to require explanation in terms of secondary, indirect or interaction factors in addition to drug specificity.

(Author's Abstr.)

The Adjunctive Use of an Intravenous Amphetamine Derivative in Psychotherapy

1. The use of intravenous Methedrine is a valuable addition to the psychiatrist's armamentarium. The comparative freedom from any dangerous complications permits its general application.

2. In the appropriately selected individual verbalization of otherwise unacceptable material promotes a better understanding of his difficulties. The cathartic effect and the newly gained insight enhance the chances of a faster recovery.

3. The best response was found in the more severely inhibited individuals, irrespective of the diagnostic label.

4. With adequate preparations and certain precautions intravenous Methedrine could also be used in the general practice of medicine.

(Author's Abstr.)

The Effect of a Distractor on the Rate of Conditioning of Normal Subjects and Patients Suffering Anxiety

Welch and Kubis (8) found a highly significant difference in the rate of conditioning the psychogalvanic reflex to a nonsense syllable paired with a buzzer between normals and patients with pathologic anxiety. Adding a wire-recording, which either gave instructions to concentrate, or emitted a continuous "E" sound, to the Welch and Kubis procedure, resulted in the following:

1. There was a statistically significant decrease in the rate of conditioning in both normals and patients, as whole.

2. There was no longer a statistically significant difference between the conditioning rates of normals and patients as a whole.

3. Analysis of the rates of conditioning of patients with varying clinical diagnoses seemed to indicate that patients with some types of illnesses (neuroses, schizophrenia) are less affected by a distractor in a conditioning situation than are others (depressions).

(Authors' Abstr.)

MARCH

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The Influence of Mescaline on Psychodynamic Material

This paper deals with the relationship of productions during mescaline intoxication to psychodynamic material obtained in drug-free psychotherapeutic sessions. The 59 patients in the study include 17 with pseudoneurotic schizophrenia (Group I), 26 with more overt schizophrenia, but without deterioration (Group II), and 16 deteriorated schizophrenic patients (Group III). It was found that the pseudoneurotic group was more accessible to study both in the drug-free and the mescalinized states, while the deteriorated schizophrenics were least accessible. Confirmation or elaboration of dynamic material obtained in the drug-free state was relatively common in mescalinized patients in Groups I and II while confirmation of dream material occurred less frequently and the appearance of new material was noted in only half of the patients in Group I and a quarter of Group II. The findings in Group III were minimal with reference to these types of data. The ego defenses are weakened and simplified during mescalinization and the patient is aware of much more frank and acute anxiety. Social and sexual behavior is less inhibited. Much of the elaboration of material represents an expansion of previous condensations. Displacement of affect from usual content to somatic discomfort was frequently observed. The mescaline hallucinations include definite scenes which appear to be specific to the patient's personality and contain material which had been condensed and repressed in the drug-free state. The present study suggests that mescaline has a definite effect on dynamic material and presents a useful technique for investigating personality structure. Its value in therapy is not evident at the present time.

(Author's Abstr.)

Clinical Effects of a "Stimulant" Barbiturate in Schizophrenics

The "stimulant" barbiturate, sodium 1,3-dimethylbutyl ethyl barbiturate, was administered intravenously to 20 patients with various forms of schizophrenia in a preliminary assay of its therapeutic value.

1. The drug exerted an irregularly occurring therapeutic effect (55·0 per cent) which was of most complete degree in pseudoneurotic schizophrenics. It has not been deemed advisable to establish further the therapeutic efficacy because of the relatively high toxicity which would preclude therapeutic application.

2. In accord with the literature that the drug is a convulsant in animals, 2 patients in this series had myoclonic seizures; in the remaining subjects the dosage was maintained at a subconvulsant level. A small minority of subjects showed weak signs of central nervous system depression in the form of slight drowsiness; the central-depressant action has not been reported in animals.

3. The therapeutic effect of the drug usually occurred independently of its weak and infrequent central-depressant action. No evidence was obtained that the drug acted as a "psychic stimulant" in the sense of heightening of mood and psychomotor processes.

4. Several explanations of the mechanism of the therapeutic action were offered and the desirability of further investigation of the stimulant barbiturate series indicated.

(Author's Abstr.)

APRIL

Sociopsychologic Factors in Hysterical Paraplegia. *Brown, W., and Pisetsky, J. E.* .. 283
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The Hypophysis Cerebri in Psychosis

1. One hundred hypophyses from mentally ill patients were examined post-mortem by means of saline suspensions under oil immersion, dark contrast, phase microscopes at magnifications of 970 diameters. Handling and equipment were sterile.

2. Suspensions of distal and neural parts were made by placing a drop of sterile saline on a wide microslide, and gently dipping a cut surface of the gland in the drop to make a turbid suspension. Coverglass was sealed to the slide with Vaseline.

3. Immense numbers of living and dead zoospores were seen in all their variations in the cytoplasm of secretory cells and pituicytes.

4. Two alternate generations of zoospores were found in all parts of the gland in various stages of development.

5. The first generation came from small brown or purple, globular cysts or spore-cases which were lodged in the cytoplasm of the hypophysial cells. The spore-cases became pigmented and sporulated: they gave rise to fine pigmented, dot-forms or elementary bodies, which invaded the surrounding cytoplasm where they formed a colony. The dot-forms were seen as fine, black dots surrounded by a clear space within a thin membranous enclosure.

6. The small dot-forms grew into large ring-forms with a clear center inside of a purple ring, and an outside enclosure. Many of these ring-forms died and became crinkled lipofuscin granules.

7. The second generation was a development of some large ring-forms into large sacs. The clear center was filled with a thick brown secretion. In this, a filament developed. At first it was short and smooth, then long and segmented and finally it broke up into globules. The brown secretion became blue-green and was used up during this period of growth of filament into globules. It was replaced by dark pigment between the globules. These round bodies escaped from the sac to form swarms of freely moving globules. They were pink-brown or purple in color, and entered the hypophysial cells. In the cells they formed a new crop of pigmented spore-cases that sporulated and gave rise to the dot-forms of the first generation.

8. Some ring-forms gave rise to large, purple, angular gamete cysts with a pigmented eye on their inside and one or two flagella with which they explored vigorously.

9. Statoblasts or resting seeds were composed of the brown substance filled with globules. Hooks of flagella projected from the surface and often gave rise to short, stout, moving filaments. Statoblasts were a resting seed. They gave rise to mucoid sacs.

10. Mucoid exudates exuded from opened enclosures in damaged colonies. They attracted and collected wandering zoospores which entered them and became small resting spores. Zoospores had a number of ways of insuring widespread propagation, transport, attachment and survival under various conditions.

11. New crops of zoospores overlapped old ones. Growth was slow, from nine to 13 years, for the two generations. Cell cytoplasm was locally destroyed; what remained was normal.

12. Zoospores appeared to be blue-green algae of Nostoc species. Dead colonies in ring stage of development were surrounded by fat to form lipofuscin granules.

(Authors' Abstr.)

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Memory Disturbances in Third Ventricle Tumours

One hundred and eighty patients with verified intracranial lesions have been interviewed by psychologists in a neurosurgical unit in order to ascertain whether there is any area of the brain the destruction of which is specifically associated with impairment of memory.

The data obtained have been analysed from three aspects: (*a*) Four cases in which impairment of memory and site of lesion were clearly defined and well localized are described in detail; (*b*) the incidence of memory disturbances in tumours of the third ventricle has been compared with that in other well localized intracerebral tumours; (*c*) patients with obvious and clear-cut defects of memory have been examined for the most common site of lesion.

All analyses support the conclusion that memory impairment is most common and specific when the area surrounding the floor and walls of the third ventricle is disturbed.

The relationship between memory disturbances and other possible causal mechanisms is briefly discussed.

(Authors' Abstr.)

A Rare Presenile Dementia Associated with Cortical Blindness (Heidenhain's Syndrome)

A case is described which was characterized clinically by a rapid course, cortical blindness, and dementia. Pathologically there was a diffuse cortical degeneration with particular emphasis on the occipital cortex, in which there was a spongiose state.

The condition closely resembles that previously described by Heidenhain, which has been classified as belonging to the Creutzfeld-Jakob syndrome.

In order to distinguish Heidenhain's and the authors' cases from other varieties of the Creutzfeld-Jakob group, the name "Heidenhain's syndrome" is suggested.

(Authors' Abstr.)

Autonomic Changes After Unilateral Leucotomy

Autonomic reflexes have been studied in four patients before and after unilateral leucotomy. The results provided no evidence of the presence of prefrontal cortical autonomic centres for the focal control of vascular or sweating responses. However, changes in responsiveness, different in sign in different subjects, support the suggestion that the frontal lobes exert both inhibitory and excitatory influence on centres which do have focal autonomic functions. Earlier experimental work and clinical observations suggest that such cortical autonomic control is centred around the sensorimotor areas.

(Authors' Abstr.)

A Comparison of Isoniazid with Modified Insulin Therapy in Neurotic States

An investigation was carried out in two groups of male subjects to test the relative merits of isoniazid and modified insulin therapy in the physical treatment of neurotic disorders.

In the group of subjects undergoing modified insulin therapy there was a significantly greater increase in weight than was to be found in the group treated with isoniazid. This observation was supported by the subjective response of the patients to treatment and was in agreement with the clinical impressions of those in charge of the investigation.

Reference is made to the possible mode of action of isoniazid in inducing a rapid gain in flesh in tuberculous and non-tuberculous conditions.

It is concluded that isoniazid is unsuitable as a substitute for modified insulin therapy in the treatment of neurotic states.

(Author's Abstr.)

Rapidly Progressive Cerebral Degeneration (Subacute Vascular Encephalopathy) with Mental Disorder, Focal Disturbances, and Myoclonic Epilepsy

A clinical, electroencephalographic, and pathological description is given of two cases of a rapidly fatal illness in late adult life in which myoclonic epilepsy and progressive impairment of consciousness were striking features. The EEG showed an unusual pattern of recurrent sharp-wave discharges over both hemispheres, and its significance in relation to the histological findings is discussed. In both patients death ensued within 15 weeks of the onset of the illness. In one there was a marked status spongiosus of the cortex, a general loss of cortical neurons, marked glial overgrowth, and numerous acute softenings in the basal ganglia. In the other, similar but less marked cortical changes were present. A vascular aetiology is postulated for the cerebral lesions, and for rapidly progressive cases of this type the name subacute vascular encephalopathy is suggested. Cases in the literature which are possibly similar are briefly discussed.

(Authors' Abstr.)

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A Persisting Change in Palmar Sweating Following Prefrontal Leucotomy

Studies on palmar skin resistance (palmar sweating) have been carried out on 16 patients undergoing bilateral standard leucotomy, four undergoing unilateral leucotomy, and three undergoing rostral cortical undercutting.

A group of 12 patients subjected to standard leucotomy showed post-operatively a significant increase in skin resistance which was present, though to a diminished extent, more than six months after leucotomy (mean follow-up time two years). This effect was not detected in the group of seven patients undergoing minor psychosurgical procedures.

Individual studies showed that the alterations in skin resistance which followed prefrontal leucotomy were related to the changes which occurred in the mental state. They were not related to changes in thermo-regulation.

The literature on the effects of prefrontal leucotomy on palmar skin resistance is reviewed.

(Authors' Abstr.)

The Effect of Cardiazol Convulsions on the Distribution and Activity of some Phosphatases in the Area Postrema of the Rat

The effects of "cardiazol" convulsions upon the distribution and activity of enzymes hydrolysing adenosine triphosphate, adenosine monophosphate, aneurin pyrophosphate, and glycerophosphate in the area postrema of the rat are described.

There are clear differences between the cytological enzyme activity observed in the normal animal and in the animal injected with "cardiazol".

The significance of the normal distribution of enzyme activity and of the changes after "cardiazol" convulsions is discussed.

(Authors' Abstr.)

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Nature of Potentials Associated with Synaptic Transmission in Lateral Geniculate Body of Cat. *Bishop, P. O., and McLeod, J. G.* 387

Thalamic Loci of Electrical Activity Initiated by Afferent Impulses in Cat

1. This paper presents a study of the characteristics of thalamic activity evoked in the cat by electrical stimulation of afferent pathways and mechanical stimulation of various skin areas.

2. The thalamic activity is characterized by the time relations and amplitudes of the potentials, their loci and their causative afferent pathways.

3. Responses in the thalamus evoked by stimulation of any pathway are located primarily in the ventral posterior nucleus, but are only poorly localized in that nucleus. Evidence for the relative absence of localization is derived from a number of sources: (*a*) At a given locus in the nucleus responses are observed as a consequence of activation by several afferent nerves or tactile stimulation of different skin areas, ipsilateral as well as contralateral. (*b*) The activity evoked via one afferent path interacts with activity evoked from another source.

4. The findings reported here, which indicate relatively poor localization within the thalamus, are discussed in relation to opposed findings of precise localization.

(Authors' Abstr.)

Relations Between Caudate and Diffusely Projecting Thalamic Nuclei

A study of alterations in the electrical activity of the forebrain induced by stimulating the head of the caudate nucleus, in cats under nembutal anesthesia, has revealed two major projections from this part of the basal ganglia.

One of these to stations along a descending extrapyramidal pathway confirms the generally held view that the basal ganglia function in the motor sphere.

A second major system of connections passes to the diffusely projecting nuclei of the thalamus. Upon caudate stimulation, burst-tripping, driving or desynchronization can be recorded from these nuclei and from cortical regions with which they are connected.

The findings indicate the important functional significance of pathways from the basal ganglia to the thalamus revealed by the anatomical studies of Ranson and Papez a decade ago. They suggest that in addition to their motor function, the basal ganglia may participate in regulating the electrical activity of the brain and hence may play a role in more general cerebral processes.

(Authors' Abstr.)

Absence of Color Vision in Cat

This experiment was designed to assess the color vision of cats. The test situation was arranged so that discrimination of spectral composition would be facilitated, but with controls for odor, position, and luminance cues. In 1,000 trials the cats were unable to distinguish between red and green; in a subsequent 1,000 trials they failed to discriminate between green and blue. A brightness discrimination was formed under the same conditions within 200 trials. It is concluded that cats are completely color-blind. This finding is consistent with the dominator-modulator theory, but not with the laminar theory in its present form. It does not support the inference that potentiation of electrocortical responses to geniculate stimulation indicates the presence of a trichromatic mechanism in this species.

(Authors' Abstr.)

Central Influences on Spinal Afferent Conduction

1. In curarized cats it has been shown that stimulation of various central structures influences the size of an afferent volley evoked by a dorsal root stimulus and recorded from dorsal and ventral columns, midbrain, cerebellum and sensory cortex.

2. The relayed response in the dorsal column and the dorsal root reflex were invariably depressed by stimulating certain central structures. The afferent volley in the ventral column as well as the afferent response in the midbrain, cerebellum and sensory cortex was depressed by similar stimulation. The primary afferent spike in the dorsal column was unchanged, however.

3. Depression of the test responses has been obtained by stimulating the bulbar and midbrain reticular formation, the ventral part of the anterior vermis, the postcentral sensory cortex, the second somatic sensory area, the precentral motor cortex and the anterior part of the cingulate gyrus. So far, no increase in the afferent response, except as a rebound, has been seen on stimulating these structures.

4. The effect of the central stimulation upon the afferent responses was completely abolished by a moderate dose of anesthesia. Anesthesia also caused a marked increase in the control size of the afferent ventral column response. A similar effect was produced by a high transection of the spinal cord in curarized animals.

5. It is concluded that synaptic afferent transmission in the spinal cord can be influenced in a physiological manner by descending pathways from certain structures in the brain. Furthermore, this sensory-regulating mechanism can evidently act in a tonic fashion.

(Authors' Abstr.)

Shivering Suppression by Hypothalamic Stimulation

Electrical stimulation of certain points within the hypothalamus of shivering cats under pentobarbital anesthesia causes a sudden termination of shivering. The anatomical region within the brain stem from which this suppressor effect can be evoked has been mapped by the use of the Horsley-Clarke stereotaxic apparatus, and the region extends throughout the hypothalamus and midbrain. The most sensitive region for shivering suppression, without the complications of movement, is the preoptic region of the hypothalamus. It is proposed that the suppressor effect is a mechanism for suppression of shivering when the musculature is needed for skeletal movement.

(Authors' Abstr.)

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Speech Disturbance in Association with Parasagittal Frontal Lesions

1. Impaired language function of varying degree and type and convulsive seizures characterized by vocalization may occur in patients with lesions of the medial portion of the frontal lobe of the dominant cerebral hemisphere.
2. The clinical features of 11 cases in which disturbed speech occurred in association with parasaggital tumors are presented and similar findings in other reported cases are cited.
3. Reports of language disorders after interruption of the anterior cerebral artery of the dominant cerebral hemisphere are noted.
4. Electrical stimulation studies of mesial cerebral cortex suggest a neurophysiological basis for language difficulties associated with lesions of the medial portion of the dominant cerebral hemisphere.

(Authors' Abstr.)

MAY

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Water Exchange in the Brain and Cerebrospinal Fluid

1. Small amounts of D_2O can safely be put into the cerebral ventricles without causing abnormalities in the EEG or general clinical status of a patient.
2. In the normal state D_2O placed in the cerebral ventricles is in equilibrium with the total body water in about 3 hours.
3. The D_2O exchange half-times after intraventricular D_2O were in very good agreement with the D_2O appearance half-times after intravenous D_2O.
4. In obstructive hydrocephalus, the tracer appearing in the lumbar region is probably carried there by the blood after being absorbed from the ventricle.
5. In spite of the upset of physiological status following an intraventricular injection of saline, there seems to be very little gross movement of CSF in an infant with non-communicating hydrocephalus.
6. Studies on patients with non-communicating hydrocephalus and on patients with communicating hydrocephalus undergoing subarachnoidureterostomy show that the exchange of water is independent of the accumulation of CSF.

(Author's Abstr.)

Anterior Cingulectomy in Man

1. After an account of its introduction and development, the technique of anterior cingulectomy is described.

2. A series of 50 cases is reported. The best clinical results are found in cases of intractable irritability, aggressiveness, violence, and agitation, especially when associated with chronic epilepsy. Patients with obsessive-compulsive neurosis also react very favorably to cingulectomy. The follow-up period extends from 5½ years to 6 months.

3. Cingulectomy is seldom followed by a significant post-operative clinical syndrome during the first weeks, in contrast with the "frontal" post-operative syndrome often observed after topectomy of the convexity.

4. A psychological study, with objective behaviour tests, discloses after cingulectomy no lowering at all of intelligence, no indication of augmented extraversion, a decrease in neuroticism, and a marked decrease in psychoticism.

5. The main EEG findings after cingulectomy are given. Chronic epilepsy is often improved by the operation.

6. The main physiological interest of anterior cingulectomy seems to be the now well-substantiated suggestion of a difference in function between dorsal granular cortex (areas 9 and 10) and mesial agranular cortex (area 24).

(Author's Abstr.)

The Increasing Importance of Lung Cancer as Related to Metastatic Brain Tumors

Pulmonary carcinoma, which very definitely seems to be undergoing an absolute increase in frequency, accounted for almost one-fourth of the metastatic tumors of the brain in this series, and must be given very serious consideration in attempting to locate the primary site of a metastatic lesion. Carcinoma of the breast, however, is the most frequent primary site in females, and accounted for exactly half of the metastases in the females in this series. The necessity of careful study of the lungs in patients showing symptoms of cerebral tumors was further emphasized by the finding of either primary or secondary cancer in the lungs of 77 of the 102 patients.

(Author's Abstr.)

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Failures of the Rorschach Technique

This review of the failures of the Rorschach technique has found the following outstanding relationships:

1. Global evaluations of the Rorschach seem to work when the Rorschach worker and the clinician work closely together.
2. Atomistic evaluation, as well as global, of the content of the Rorschach protocols (as distinct from the perceptual scoring) seem to work.
3. Atomistic analysis of the perceptual factors is a failure.
4. Factor analysis of atomistic scores of both the perceptual as well as the content variety, seems to work.

The best hypothesis to explain these four facts is that the Rorschach is an interview and that its correct evaluation, like the correct evaluation of any interview, is dependent upon its content. If we provide scales for analyzing its content, we shall be well on the way towards clarifying many of the present day contradictions and obtain a better perspective on the evaluation of personality.

(Author's Abstr.)

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Metabolic Reactions to Cold Stress of Rats with Hypothalamic Lesions

By means of a newly devised stereotaxic instrument, lesions were placed in various areas of the hypothalami of Sprague-Dawley albino rats with electrodes which traversed the brain from side to side in the horizontal plane. Such lesions resulted in a high mortality rate and produced various hypothalamic syndromes in many surviving animals.

Upon evaluation of the physiologic and anatomic data it was found that the operated animals fell within four groups:

1. Animals with posterior hypothalamic lesions showed a high oxygen consumption rate and a relatively normal body temperature.
2. Animals with dorsal tuberal hypothalamic lesions demonstrated low oxygen consumption rates with low body temperatures.
3. Animals with ventral tuberal hypothalamic lesions did not exhibit any change in oxygen consumption rates or body temperatures.
4. Animals with anterior hypothalamic lesions showed gradual falls in oxygen consumption rates and a concomitant gradual lowering of body temperatures.

(Authors' Abstr.)

Present Concepts in the Treatment of Purulent Meningitis

In summary, there are a number of principles which should be followed if the optimum results in the treatment of purulent meningitis are to be achieved and if disabling sequelae are to be reduced to a minimum:

1. Early diagnosis of the infection, both clinical and bacteriologic.
2. Proper choice of antibiotic agents.
3. Prompt institution of therapy, rapidly achieving and maintaining high serum and cerebrospinal fluid levels of two complementary acting antibiotics.
4. Avoidance, when possible, of dangerous drugs and unnecessary intrathecal injections which may be injurious to the patient.
5. Elimination of focal suppurative lesions.
6. Early recognition of possible complications, such as subdural effusions, relapse of infection, or development of hydrocephalus.
7. Supervision of the total needs of a patient critically ill with purulent meningitis.

(Author's Abstr.)

Experiences With RO-2-3059 as an Anticonvulsant

RO-2-3059, a new benzhydryl derivative with anticonvulsant properties, has been used alone and in combination with phenobarbital in 43 patients in the neurology out-patient clinic of the Ohio State University College of Medicine. These were comprised of patients with grand mal, petit mal, and temporal lobe seizures, singly or in combination. A combination of RO-2-3059 with phenobarbital was chosen for continuing therapy in approximately 40 of these, in view of symptoms suggesting excessive central nervous system stimulation when RO-2-3059 was given alone. Of the original group of patients so treated, 20 have continued follow-up observation; this report covers the details of treatment and observations for the preceding six months. In eight patients of this group, the RO-2-3059 and phenobarbital combination was the sole anticonvulsant agent; the remaining 12 received one or more additional anticonvulsants or supplementary doses of phenobarbital as adjunctive therapy. The observations included repeated physical examinations and blood counts; in several instances the effects of discontinuing medication temporarily were also determined.

In general, RO-2-3059 combined with phenobarbital was found to be moderately effective against grand mal seizures, rather ineffective against temporal lobe attacks, and relatively ineffective or perhaps worthless against petit mal attacks. Side effects were mild even at high dosage levels, and consisted chiefly of nervousness, low amplitude muscle tremors, and euphoria; this last feature was considered in most cases as more of an advantage than otherwise.

On the basis of limited experience to date, RO-2-3059 in combination with phenobarbital is considered worthy of more extensive study.

(Author's Abstr.)

Spontaneous Rhythmic Ocular Movements

The occurrence of spontaneous rhythmic eye movements is described. Their possible relationship to mental concentration is discussed. It is suggested that these eye movements may lend themselves to further clarification by means of electroencephalographic studies.

(Author's Abstr.)

Cerebrospinal Fluid Changes Following Closed Cranio-cerebral Injuries

1. In a study of 43 patients with a closed head injury, the protein level was the most accurate cerebrospinal fluid guide to the severity of cranio-cerebral injury. The frequency of protein elevation generally varied directly with the length of unconsciousness. The level was increased in patients with permanent neurologic deficits and those who had neuropsychiatric disturbances.

2. When the determination was made within 90 hours following injury, the cerebrospinal fluid sugar value varied inversely to the period of unconsciousness and indicated the acuteness of the craniocerebral injury.

3. The presence of more than 100 erythrocytes per cu. mm. in the cerebrospinal fluid was not a reliable guide to the severity of the craniocerebral injury with absence of fracture through the calvarium. Protein elevations were usually independent of the elevated number of red cells in the cerebrospinal fluid.

4. There was no correlation between the state of consciousness and the intracranial pressure. However, most of the patients who had headaches following injury had an increased manometric reading.

5. The chloride level of the cerebrospinal fluid was of little diagnostic importance in closed craniocerebral trauma, but did show a change following severe vomiting.

(Author's Abstr.)

Isolated Fear

Seven cases, consisting of two meningiomas, four gliomas, and one aneurysm, each with a feeling of unaccountable fear as an aura, are presented. Three similar cases from the literature are cited.

It is concluded that the aura of fear in symptomatic epilepsy has a focal significance, indicating abnormal physiologic activity in the temporal lobe on either side. It is suggested that localization for the neuronal mechanism which, during epileptic activity, results in the aura of fear is on the medial aspect of the temporal lobe. The cortical portion of the mechanism of the emotions proposed by Papez is also considered in this situation.

The importance of a consideration of the aura of fear rests not merely in that it might be the initial symptom of a gross and at times reversible underlying cerebral pathology, neoplastic or vascular; knowledge concerning the physical basis of the emotions, which play such an important role in the realm of human behavior and endeavor, is still limited. A study of cases such as these affords an approach along physical lines to the study of at least one form of emotional activity in man.

(Author's Abstr.)

Epileptic Sleep Terrors

Electroencephalographic studies of a large group of patients experiencing sleep terrors have confirmed Robin's clinical concept. Two types of sleep terrors may be distinguished: (1) epileptic sleep terrors during which the patient is unconscious and for which there is amnesia, and (2) terrifying nightmares, or banal or common sleep terrors in which unconsciousness and amnesia are only partial.

In cases of banal or common sleep terrors studied, the electroencephalogram was normal and the family and personal histories were negative for epilepsy. Psychologic studies in these cases showed existence of neurotic conflicts.

As stated by Robin, unconscious and amnesic sleep terrors are clinical manifestations of epilepsy, which the authors' studies indicate is associated with a cortical focus in the parietotemporooccipital region. This has been proved by the following facts: (1) 94·5 per cent of cases with this type of sleep terror showed abnormal focal activity in the parietotemporooccipital region in interictal records; (2) in ictal records they showed epileptic discharges originating in the same region; and (3) in one case of sleep terrors with a focus in the parietotemporooccipital region, terrors disappeared after removal of the focus.

Clinically, sleep terrors are considered automatisms preceded by terrors and are classified with secondary automatisms. Terrors are a minor manifestation of an epileptic discharge originating in the temperoparietooccipital region.

Differentiation between epileptic sleep terrors and other types of automatisms, especially simple sleep walking, may be made. The latter may be physiologic and may show normal electroencephalographic records, or may be due to an epileptic attack precipitated by an epileptic discharge originating outside of the parietotemporooccipital region.

Clinical differential diagnosis between epileptic and banal or common sleep terrors is difficult, and the electroencephalogram may be used to distinguish between them.

(Authors' Abstr.)

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Headache. Studies by Means of the Basal Electroencephalogram

In 61 individuals electroencephalographic studies were obtained applying a new technique for the recording from the base of the brain.

Thirty-six patients were suffering with headache, and there were 25 normal subjects. The basal brain activity found has been arbitrarily divided into three grades: I, low voltage symmetrical type; II, higher voltage, 7-14 waves per second, usually asymmetrical, dominant in the left side; III, when the latter activity becomes intermingled with sharp waves or spikes.

Both Grades II and III increase during mental activity and emotional conflict. This so-called basal rhythm has been found in 28 per cent of normal subjects, in 30 per cent of simple headache, and in 61·5 per cent of the migraine group. The basal rhythm of Grade III has not been found in our normal subjects.

The rhythm described is probably an electrical activity related to a function of the rhinencephalic area including the temporal lobes.

(Authors' Abstr.)

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The Effect of Thiamin Deficiency Produced by Oxythiamin, by Neopyrithiamin, and by Diet, on the Metabolism of Alcohol

Doses of ethyl alcohol (1 g. per kg. of body weight) which produced only mild intoxication in normal dogs resulted in severe illness or death when given to dogs pretreated with oxythiamin. This increased toxicity of alcohol after oxythiamin was accompanied by a marked fall in blood glucose but the blood acetaldehyde did not increase.

A slow intravenous infusion of acetaldehyde also produced a fall in blood glucose in oxythiamin-treated dogs but did not change the glucose level of the blood in normal animals.

Dogs treated with neopyrithiamin or made thiamin-deficient by means of a thiamin-free diet were only mildly intoxicated by 1 g. of alcohol per kg. and both their blood glucose and blood acetaldehyde remained within normal limits.

The rate at which alcohol disappeared from the blood in all their treated dogs was unchanged from that found in the same animals without treatment.

These results are interpreted as evidence that thiamin plays some role in the usual pathway for the metabolism of acetaldehyde (stage II of alcohol metabolism), and that this role is beyond the first step in the metabolism of acetaldehyde.

(Authors' Abstr.)

Investigations of the Acid-base Balance of the Blood During the Disulfiram-Alcohol Reaction

The normal pH of the blood of human subjects after half an hour at rest was determined as 7·445 in arterial blood and 7·413 in venous blood.

After intake of alcohol alone a distinct shift toward increasing acidity was observed, accompanied by lowered values of bicarbonate (acidosis). There were no accompanying changes in the electrocardiogram.

In subjects pretreated with disulfiram, intake of alcohol was followed by a constant shift toward the alkaline side. This shift is typical of the disulfiram-alcohol reaction and is accompanied, as a rule, by reduction of the carbon dioxide content of the blood. It is emphasized that the condition is an alkalosis.

The pH of the blood tended to increase with increasing doses of disulfiram up to a total dose of 3 g. during the 3 days preceding the experiment.

(Author's Abstr.)

1. Biochemistry, Physiology, Pathology, etc.

Oxidative Deamination of L-Glutamic Acid in Brain Homogenates. Klein, E. E. [*Soobshcheniya Akad. Nauk. Gruzin., S.S.R.* **13,** 273 (1952).]

Homogenates of hamster brains were prepared in 1·1 per cent aq. KCl. Data are for 30-minute runs in a Warburg respirometer at 0°. By using K phosphate buffer at pH 7·3 maximum. Qo2 was at 0·04 M PO_4^{3-}; similarly, optimum concentration of adenosinetriphosphate was 0·03 M. The addition of codehydrase 1 (I) and preparations containing diaphorase and cytochrome c (II) accelerate the deaminative oxidation. Nicotinamide is of value in that it inhibits decomposition of (I). (II) alone has no influence on the reaction.

J. P. DANEHY (Chem. Abstr.)

Evidence for a Neutral Proteinase in Brain Tissue. Ansell, G. B., and Richter, D. [*Biochim, et Biophys. Acta,* **13,** 92 (1954).]

Fresh rat-brain tissue was shown to contain a system which liberates amino acids on brief incubation at pH 7·4. The system is unstable; it is active for only 1-1·5 hours after death. The amino acids are not derived from a simple peptide or polypeptide present in the brain tissue; at least 9 different amino acids were liberated and the peptide-bound N in the tissue did not decrease. It is concluded that the amino acids are released by the action of an intracellular proteinase active at pH 7·4. The system is not activated by 0·01 M cysteine or KCN, and is almost completely inhibited by 0·01 M 1 CH_2COO^- or 0·005 M $CuSO_4$. It is 75 per cent more active in the gray matter than in the white matter of rabbit brain. Its initial activity in the rat brain resulted in the release of 1·8 γ amino N/mg. dry wt./hr., which rate fell off rapidly.

MORTON PADER (Chem. Abstr.)

Proteolytic Activity of Brain Tissue. Ansell, G. B., and Richter, D. [*Biochim. et Biophys. Acta,* **13,** 87 (1954).]

The properties and activities of the cathepsin (1) in human and other brain tissues were investigated. Active (1) was found in rat, rabbit, bovine, and human brain in the following concentrations ((1) units/g. dry wt. × 10^{-4}): rat whole brain, 32; cow cortex, 52; rabbit cortex, 31; human white matter, 12; human cortex, 72. The (1) activity of human frontal cortex and of isolated nuclei was of the same order of magnitude. (1) is stable at 4°, has maximum activity at pH 3·5–3·8, and its activity is not affected by the presence of 0·002 M cysteine, glutathione, CN^-, or 1 CH_2CO^{2-}. The presence in brain tissue of a polyepetidase and a dipeptidase was confirmed. The "gelatinase" of Takasaka was not confirmed.

MORTON PADER (Chem. Abstr.)

Insulin Tolerance and Hypoglycemic Convulsions in Sheep. Jarrett, I. G., and Potter, B. J. [*Australian J. Exptl. Biol. Med. Sci.*, **31**, 311 (1953).]

Intravenous injection into fasted adult sheep of 4 units of insulin (1) per kg., and in 1 animal 10 units of (1) per kg., failed to cause convulsions even though the concentration of blood glucose was reduced to very low levels for long periods. Adult splanchnicotomized sheep were more sensitive to (1) injected intravenously and convulsions resulted after a single dose of 4 units of (1) per kg. The subcutaneous injection of 3–5 units of (1) per kg. into adult sheep was followed by long periods of hypoglycemia terminating in severe and prolonged convulsions. Once the convulsions have begun, after subcutaneous (1), apparently an irreversible state was often reached which was usually refractory to intravenous glucose therapy in spite of a return to normal blood glucose level. Young lambs were much more sensitive to intravenous (1) than adult sheep. As the lambs became older, their tolerance to (1) increased. Young lambs behaved like nonruminants in their response to both intravenous and subcutaneous (1).

N. R. STEPHENSON (Chem. Abstr.)

Analeptic Effect of Succinate in Coma and in Confusional States. Trautner, E. M., and Trethewie, E. R. [*Med. J. Australia*, **2**, 848 (1953).]

Guinea pigs were injected intraperitoneally with 25–75 mg. of Na pentobarbital (I)/kg. Half of the animals were given 3·0 ml./kg. of an 18 per cent solution of anhydrized Na succinate (II) by intraperitoneal, intravenous, or intracardiac injection. If the dose of (I) was above the LD_{80}, no life-saving effect of (II) was detected. With doses of (I) around the LD_{50} or less, the injection of (II) soon after the onset of narcosis caused only a temporary restlessness. With LD_{10} to LD_{20} doses of (I) the injection of (II) caused non specific signs of a temporary lightening of narcosis. In rats the results were similar, except that with the lighter doses of (I) the injection of (II) shortened the period of narcosis. In a few experiments on cats and dogs no consistent or outstanding effects of (II) were observed. In normal humans the slow intravenous injection of 50–100 ml. of a 5 per cent solution of anhydrized (II) caused a short spell of coughing, increased strength and (or) frequency of the radial pulse, and deepened respiration. A red flush occurred in the sweat area of the cervical sympathetic. The injection of 30–50 ml. of the 5 per cent solution into schizophrenics undergoing insulin treatment caused a transient lightening of the hypoglycemic coma. In prolonged insulin coma, where intravenous glucose was ineffective, 100–150 ml. of 5 per cent (II) wakened the patients. Patients under thiopental narcosis were readily awakened by the injection of (II). Manometric experiments with guinea-pig brain failed to reveal any stimulating effect of (II) on respiration other than that due to the oxidation of (II) itself.

E. DONALD GRAHAM (Chem. Abstr.)

Migraine: Laboratory Findings and the Prophylactic Managements of Patients with Hypoglycemia. Earle, Sister M. P. [*Australasian J. Med. Technol.*, **2**, *No.* 2, 15 (1953).]

A selected group of 300 migraine patients were shown to have a permanently low blood-sugar level, even when in complete health (30–120 mg/100 ml. blood, as compared with 80–170 for normal persons). The symptoms were caused by ketosis resulting from the low sugar, with a consequent fall in pH and disturbed water balance. Patients responded to a diet of selected carbohydrate foods of moderately high caloric value, moderate protein, and low fat.

G. J. WYLIE (Chem. Abstr.)

Cerebral Hemodynamics and Metabolism in Subjects over 90 Years of Age. Fazekas, J. F., et al. [*J. Am. Geriatrics Soc.*, **1**, 836 (1953).]

The cerebral blood flow and metabolic rate of 18 subjects, 90–102 years of age, were lower than in normal subjects who were under 50 years, but the same as in normal subjects 50–91 years of age. Correlation between the mental status of the subjects and cerebral blood flow or metabolism was not good.

THERESA SEVERN (Chem. Abstr.)

Spreading Factor and Mucopolysaccharides in the Central Nervous Systems of Vertebrates. Bairati, A. [*Experientia*, **9**, 461 (1953).]

Modification of the cohesive material among nerve-cell bodies, fibers, glia, and blood vessels with hyaluronidases and positive Hotchkiss reactions and metachromasia tests strongly indicates that mucopolysaccharide substances exist in the intercellular spaces of vertebrate central nervous systems.

D. S. FARNER (Chem. Abstr.)

An Ultramicrospectrophotometric Study of the Purkinje Cells of the Albino Rat. Attardi, G. [*Experientia*, **9**, 422 (1953).]

The anterior lobe of vermis cerebelli was treated by freezing-drying method imbedded in paraffin, and sectioned. Absorption measurements were effected on sections immersed in glycerol. Cytoplasmic ultraviolet extinction values at 2650 and 2800 A. for individual cells showed rather pronounced modal values, about 0·14 and 0·1, respectively. Digestion with protease-free ribonuclease preparation caused a reduction in extinction values at 2650 and 2800 A. Reduction of extinction values at 2650 A. is assumed to be the result of loss of pentose nucleic acid (PNA) and to a lesser extent of protein attached to PNA. The reduction of extinction at 2800 A. is due to the same but primarily to loss of protein bound to PNA.

D. S. FARNER (Chem. Abstr.)

Detection of New Abnormal Metabolites in the Urine of Phenylketonuria. Boscott, R. J., and Bickel, H. [*Scand. J. Clin. and Lab. Invest.*, **5**, 380 (1953).]

Two-dimensional paper chromatography of the phenolic acid fraction 1 from the urine of children with phenylketonuria showed deviation from the normal pattern. $C_6H_5CH_2COCO_2H$ (I) was detectable when the patients received a normal diet or daily supplements of 1–10 g. DL-phenylalanine (II) but disappeared on a (II)-free diet. Large amounts of p-$HOC_6H_4CH_2CO_2H$ (III) and lesser amounts of p-$HOC_6H_4CH_2CH(OH)CO_2H$ (IV) were consistently found in the urine of all phenylketonuric urine. The ortho isomer of (III) was excreted in large amounts, whereas the meta isomer found in normal urine was not excreted by these patients. Fractions 2 and 3 of the urine consistently contained 5-benzalhydantoin (an artefact from (I) and urea) as well as (III) when (II) was fed, but the excretion of (IV) and (III) was unchanged. The pathway of (II) metabolism in phenylketonuria is discussed.

BERNARD KLEIN (Chem. Abstr.)

The Inhibition of Brain Hexokinase by Adenosinediphosphate and Sulfhydryl Reagents. Sols, A., and Crane, R. K. [*J. Biol. Chem.*, **206**, 925 (1954).]

Brain hexokinase preparations require free SH groups for activity as indicated by cysteine-reversible p-Chloromercuribenzoate inhibition and o-iodosobenzoate inactivation. Purified preparations of brain hexokinase are sensitive to heavy metals and are protected by metal-binding agents. Activity is maximum in the pH range 6–8. Q_{10} is 2·2 in the range 30–40° and is greater at lower temperatures. A half-maximum rate is obtained at 0·0008 M Mg. When Mg is not limiting, the half-maximum rate occurs at 0·00013 M adenosinetriphosphate (ATP). Adenosinediphosphate inhibits the enzyme competitively with (ATP). The enzyme has the same apparent affinity for both nucleotides.

FELIX SAUNDERS (Chem. Abstr.)

Influence of Phenothiazine Compounds on the Respiration of Brain Homogenates. II. Nature of the Oxidative Inhibition and Antagonistic Pharmaceuticals. Balestrieri, A., and Berti, T. [*Boll. soc. ital. biol. sper.*, **29**, 1669.]

Phenothiazine compounds, especially Largactil, inhibit glucose oxidation and that of related compounds in brain homogenates similar to phenobarbital. The latter requires 10 times higher concentration for equal effects. The oxidation of succinate is not inhibited. Methylene blue is an antagonist with respect to this inhibition.

A. E. MEYER (Chem. Abstr.)

The Exchange of Polysaccharides in Brain of Animals under Different States of Functioning. Khaïkina, B. I., et al. [*Ukraïn Biokhim. Zhur.*, **24**, 39 (1952).]

The activity of several enzymes was measured at various parts of the brains of dogs and rats for normal brain, brains in electro-convulsions, after termination of same and brains in a state of narcosis. In the gray and white marrow of a dog brain, both the phosphorylase (I) and the amylase activities increase in a state of electro-convulsions, which increase is noticed also some time after the end of the convulsions. Such convulsions cause the bound polysaccharide (II) fraction to increase up to 100 per cent, and the free (II) fraction diminishes. In rats the convulsions were caused by cardiazole, and the whole brain was taken for the determinations. The (II) exchange in both animals shows the same trend. Dog brains show under narcosis with ether (III) or evipan a (II) synthesis which does not require a primer. The (I) is much more active in the state of narcosis than in the normal state; phosphorolysis and amylolysis are somewhat lower. The amount of (II) under narcosis goes up, and the proportion of bound and free (II) remains unchanged. Rats were narcotized by aid of (III) or with hexenal (IV). Narcosis with (III) does not show any change of the (II) exchange, but a narcosis by (IV) shows an increase of the synthesis of (II) and of the activity of (I), which results in a decrease of the amount of (II), because the amount of free (II) drops. Thus narcosis affects the exchange of (II) in a multiple manner. The diminishing of the nerve functions under the experimental conditions does not always have the same effects on the dynamics of the (II) exchange, but the activity of (I) increases both in the state of convulsion and in the state of narcosis. The activity of (I) leading to a synthesis of (II), is high both in the cases of excitation and depression, whereas the activity of enzymes which split (II) is lowered in the case of depression. Any influence which diminishes the functioning of the nervous system leads to an accumulation of the bound (II).

WERNER JACOBSON (Chem. Abstr.)

Diffuse Sclerosis in an Infant: Metachromatic Leucoencephalopathy. Feigin, Irwin. [*Bull. N.Y. Acad. Med.*, **30,** 74 (1954).]

An abnormal material was deposited as granules and small globules within the tissues and phagocytes of the central white matter of the infant's cerebrum. The material was basophilic; metachromatic to toluidine blue in an aqueous medium, but not after passage through alcohol; it stained tan with phosphotungstic acid hematoxylin and blue with azocarmine; it gave positive tests with the periodic acid leucofuchsin, Sudan black, phosphomolybdic acid, Nile blue, modified acid hematin, acid-fast, and alloxanleucofuchsin methods; it was negative with the mucicarmine, Sudan IV, Feulgen, and Shultz methods; it was iostropic in polarized light, and insoluble in H_2O and organic solvents after formalin fixation. It was interpreted as a complex lipoprotein, having phosphatide and glycolipide constituents similar to those in myelin, and related to myelin formation.

THERESA SEVERN (Chem. Abstr.)

The Pathology of Tay-Sachs Disease. Aronson, Stanley M. [*Bull. N.Y. Acad. Med.*, **30,** 72 (1954).]

The primary cellular alterations resulting in this disease occur in the neurons. The neurons lose their angularity, become enlarged, and gradually dissolve because of the accumulation of pale-staining, hematoxylinophilic, refringent granules of prelipide substance. Demyelination, which occurs in the infantile disease, is probably the result of the arrest of myelin formation. As the neurons break down, large numbers of activated microglial cells, filled with intensely sudanophilic material, accumulate in areas of gray matter. The difference in staining between the neuronal prelipide and the liberated neutral lipide indicates that chemical breakdown occurs in the latter. The microglia move to neighboring perivascular areas, and finally endothelial cells become involved and distend with lipide. Parts of the retina undergo similar changes; the ganglionic cells become swollen and contain prelipide material.

THERESA SEVERN (Chem. Abstr.)

Relation Between Asymmetric Acetylcholinesterase Activities in Rabbit Brain and Three Behavioral Patterns. Aprison, M. H., et al. [*Science*, **119,** 158 (1954).]

The right common carotid artery of rabbits was injected with 0·1 mg./kg. of diisopropyl fluophosphate. The acetylcholinesterase (I) activity of the right and left frontal cortex and right and left caudate nucleus was measured 20 minutes later. In animals that had shown a definite behavior pattern of circling to the right or left, the decrease in (I) was very much greater in the right side of the brain than on the left. Animals that did not circle showed no difference between the right and left side of the brain.

J. D. TAYLOR (Chem. Abstr.)

The Quantitative Histochemistry of Brain. I. Chemical Methods. Lowry, Oliver H., et al. [*J. Biol. Chem.*, **207,** 1 (1954).]

General analytical procedures and tools are described for making various determinations with as little as 10γ of brain or other tissue. The measurement of the riboflavine in 10γ of brain (3×10^{-5} of riboflavine) is described. A method for determining chloride (4×10^{-10} mole) in 10γ of tissue is prevented; it involves the precipitation of chloride with Ag at a volume of 2·5 microliters, followed by measurement of excess Ag with 5-(p-dimethylaminobenzylidene)-rhodanine. A more sensitive means of measuring phosphate is given, together with directions for the determination of 5 P fractions from 20γ of brain.

II. Enzyme Measurements. Lowry, Oliver H., et al. [*Ibid.* 19].

Methods are described for measuring 6 enzymes with as little as 5–10 γ of brain. Adenosinetriphosphatase (I) and acid (II) and alkaline phosphatase (III) are measured with adenosinetriphosphate (ATP) and di-Na p-nitrophenyl phosphate by incubation at 10 microliters and final color measurement at 50–100 microliters. Cholinesterase (IV) is measured by the color change from acetylcholine hydrolysis in 10 microliters of a buffer-indicator pair (barbitol and phenol red) having nearly the same pK. An almost linear relation between enzyme activity and color change is achieved. Fumarase (V) is measured by determination of malate by an unpublished sensitive method of John Speck. This fluorimetric procedure has a sensitivity far in excess of present needs. Aldolase (VI) measurement is based on the macroprocedure of Sibley and Lehninger. Certain changes required on the micro scale may also be helpful for macro work. The 6 methods have a coefficient of variation of about 5 per cent with 10–20 γ of brain. All 6 enzymes were partially purified or separated from soluble components of rabbit brain and added to crude brain homogenates to test for summation of activity. No inhibition was observed, but slight enhancement was found for (II) and (VI). All 6 enzymes withstand freezing, drying, and storage up to a year at 20°. The pH optimum for (II) is more alkaline when Mg is present than without it (pH 5·9 vs. 5·3); this difference is due to the presence of 2 phosphatases, one of which has a marked requirement for Mg, with an optimum of about 6·5. (III) activity is increased about 30 per cent by Mg. (VI) is relatively pH-independent from pH 7·2 to 9·5. (I) of rabbit brain is inactive without a bivalent cation. It is 50 per cent activated by 2×10^{-4} M Mg.Ca activation is only one-third that of Mg or Mn and Ca competes with Mg and inhibits the activity when both are present. Well-defined Michaelis constituents were obtained for (II), (III), and (V): 1·58, 0·89 and 1·83 millimoles, respectively. The K_s for brain aldolase is probably not more than 10^{-5} M. The K_s for (I) is too low to determine. (I) falls off most with increasing product formation. (II) and (III) are both unstable, and are largely insoluble. The 6 enzymes have very different temperature coefficients. (IV) is least sensitive to temperature; $Q_{10}=1\cdot21$ between 10 and 38°. (VI) is the most temperature-sensitive; $Q_{10}=4\cdot1$ between 4 and 15°. The energy of activation for brain (V) at pH 6·7 is 6600 calculated at 25–38°, and 14,600 calculated at 4–15°.

III. Ammon's Horn. Lowry, Oliver H., et al. [*Ibid.*, 39–49.]

By direct microchemical procedures, 6 histologically distinct layers of Ammon's horn of the rabbit were analyzed for dry-weight protein, total lipides, 4 lipide fractions, 5 P fractions, 6 enzymes, and riboflavine. There was remarkably little range in the concentration of 14 constituents in 15 rabbit brains. The predominant type of cell body present (small pyramidal cell) is much lower in total lipides than is the rest of the brain. Its general composition resembles that of the cells of an organ such as the kidney. The dendrites are at least as rich in metabolic enzymes as are the cell bodies. They probably account for the bulk of the brain metabolism. Substantial amounts of lipides are associated with dendrites (about equal amounts of cholesterol, lecithins, and cephalins), but the question is raised whether these lipides are not in but around the cytoplasm of the dendrites. The lipides of the myelinated fibers are comparatively rich in sphingomyelin and cholesterol. Because the enzyme activity and content of acid-soluble P in the myelinated layer are larger than would be expected from the axons and glia, it is suggested that the myelin itself may be metabolically active.

F. SAUNDERS (Chem. Abstr.)

Symposium on Neurohumoral Transmission. Philadelphia, 1953. [*Pharmacol. Revs.*, **6**, 3–131 (1954).]

L. E. GILSON (Chem. Abstr.)

Progressive Changes in Acid-soluble Phosphorus Compounds During Development of the Rat Brain. Bieth, R., et al. [*Compt. rend. soc. biol.*, **147**, 1273 (1953.)]

Quantitative data are given for 6 CCl_3CO_2H-soluble P fractions of brains of rats from 3 days to 12 months old.

L. E. GILSON (Chem. Abstr.)

Alkaline Phosphatases of Nerve Cells. Irazoque, J., and Demay, M. [*Bull. microscop. appl.*, **1**, 102 (1951).]

In beef, endothelia of nerve center capillaries, molecule layer of cerebellum, Rolando's gelatinous substance of the spinal cord, spinal ganglia, capsular cells and capillaries of ganglia are rich in phosphatases (I); in superior nerve centers (I) reaction is weaker on account of the smallness of the cells but capillaries of the conjunctive tissue and Schwann membrane gave negative (I) reaction. In snail, large ganglionar and peripheric nerve cells are rich in (I) but their extensions are not.

FRANCOISE RICHARD (Chem. Abstr.)

Transformation of Glucose-1-phosphoric Acid in the Brain. Bhaïkina, B. I. [*Ukraïn. Biokhim. Zhur.*, **20**, 342 (1948).]

In a 1st series of experiments the phosphorylative splitting of glycogen (I) was studied in rabbit brain. Phosphorolysis (II) takes place only during splitting of (I). The presence of adenylic acid does not promote it. The optimum of the enzyme action lies at pH 6·2. Disappearance of inorganic P accompanies the breakdown of (I), but there is no direct relation between the amount of (I) split and the amount of inorganic P esterified. More (I) breaks down in an acetate than in a phosphate buffer, showing that the path does not necessarily include (II). In a 2nd series of experiments the formation in the brain of polysaccharides (III) from glucose-1-phosphoric acid (IV) was investigated. Two facts are noted: (I) a large synthesis of (III) takes place from added (IV), (2) several different (III) are synthesized, of the type of (I), dextrin (V), and starch (VI). More (VI) is synthesized at pH 6·2–5·7, and at 6·0–6·5 more (I). At more acid pH (V) and some (VI) are formed. Addition of NaF (VII) does not prevent the synthesis, at pH 5 it even promotes it; but (VII) does prevent a branching of the chains. The seasons of the year influence the experiments. During the summer brain will prepare from (IV) almost exclusively (I), but during the winter both (I) and (VI) will be synthesized. In a 3rd series of experiments the dephosphorylation of (IV) by phosphatase (VIII) was followed by increase of inorganic P and change of the reducing power of the glucose. (VIII) has its optimum pH at 6·7 and acts on (IV) exclusively. Thus all glucose-6-phosphate in the brain, before it can be utilized, must be transformed into (IV) by the action of phosphoglucomutase.

WERNER JACOBSON (Chem. Abstr.)

The Adenosinetriphosphatase of Brain. Palladin, A. V., and Shtutman, Ts. M. [*Ukraïn. Biokhim. Zhur.*, **20**, 311 (1948).]

The adenosinetriphosphatase (I) of brain can be extracted with distilled H_2O in the ratio 1:20. Its optimum activity is at pH 7·4–8·0. The activity of (I) in aqueous rabbit-brain extracts at acid pH is higher in glycine (II) buffer than in barbital buffer, since (II) protects the enzyme against denaturation by acids. The (I) of brain is activated by Mg^{++}, but not by Ca++. Cysteine and $1CH_2COOH$ do not affect its activity, NaF depresses it. (I) is less sensitive toward the ions of the medium than is (I) bound to myosin. The aqueous extracts of rabbit and cattle brains remove both labile phosphate groups from adenosinetriphosphoric acid; the cattle brain extracts also split adenylic acid and inosinephosphoric acid. The (I) of rabbit brain extract is bound to 2 protein fractions which can be precipitated by addition of 0·01 and 0·4 N Na_2SO_4, respectively. If extracts and precipitates are diluted with 0·01 N Na_2SO_4, the activity of (I) is increased; this does not occur if the centrifugate is diluted in the same way. Conclusion: In rabbit brain there is an inhibitor for (I) which precipitates upon addition of 0·01 N Na_2SO_4 almost completely from the aqueous extract together with part of the enzyme.

WERNER JACOBSON (Chem. Abstr.)

Phosphate Exchange in Brain Phospholipides in vivo and in vitro. Streicher, E., and Gerard, R. W. [*Proc. Soc. Exptl. Biol. Med.*, **85**, 174 (1954).]

When rat-brain homogenate was incubated at 37° in phosphate buffer labeled with P^{32}, the phospholipide phosphate reached a maximum specific activity in 20 minutes. In live rats the specific activity of the same brain fraction rose continuously for at least 20 hours after the intraperitoneal injection of $Na_2HP^{32}O_4$. When the lipide extract was divided into several fractions by different organic solvents the specific activities of these fractions were markedly dissimilar in the in vitro experiments, but were closely similar in the in vivo experiments.

L. E. GILSON (Chem. Abstr.)

The Chemical Properties of the Neurosecretory Substance in the Hypothalamus and Neurohypophysis. Schiebler, T. H. [*Exptl. Cell Research*, **3**, 249 (1952).]

Freshly fixed hypothalamus-hypophysis tissue from man, dog, cat, rabbit, cattle, rat, and fish was analyzed cytochemically. The neurosecretory substance appeared to be a glycolipoprotein complex. No species difference was apparent.

HERMANN I. CHINN (Chem. Abstr.)

Effects of Fluoroacetate Poisoning on Citrate, Lactate, and Energy-rich Phosphates in the Cerebrum. Pscheidt, G. R., et al. [*Am. J. Physiol.*, **176**, 483 (1954).]

Chemical changes in the cerebrum associated with fluoroacetate poisoning were studied in morphinized dogs, the tissue specimens being obtained after the brain had been frozen in situ. When a large dose of methyl fluoroacetate is injected there is a latent period of about 40 minutes after which the citrate in the brain increases rapidly to a maximum, which is reached soon after the beginning of epileptiform seizures. During the preconvulsive period, in which the inhibition in the tricarboxylic cycle is apparent from the rise in citrate, the metabolic block is not of sufficient degree to induce changes in the lactate, creatine phosphate, or inorganic phosphate in the cerebral tissue. During the convulsive stage the lactate is increased and some breakdown of creatine phosphate occurs. In the post-convulsive state the electrical pattern and chemical findings resemble those of extreme anoxia in that the lactate is very high and the phosphate bond energy reserves are depleted. Application of fluoroacetate to the exposed cortex induced local excitation, while application of Na citrate did not. The results support the view that neither the blocking of oxidations nor the presence of excess citrate in the brain is the cause of fluoroacetate seizures.

E. D. WALTER (Chem. Abstr.)

Effect of Adrenalectomy on the Anticonvulsant Action of Glutamic Acid in Mice. Fuller, J. L. [*Am. J. Physiol.*, **176**, 367 (1954).]

Results are consistent with the hypothesis that genetically controlled differences in seizure susceptibility in one type of mouse are mediated through metabolic differences in the central nervous system, and that the protective effect of glutamic acid may be due to a central rather than a peripheral action.

E. D. WALTER (Chem. Abstr.)

Experimental Studies on Focal Epileptic Seizure. Nakahama, H. [*J. Physiol. Soc. Japan*, **16**, 61 (1954).]

Application of isonicotinic acid hydrazide (I), absorbed in filter paper, on the cerebral cortex of cats induced seizures. (I) applied to the motor area was enough to induce generalized seizures when 0·02 mg./sq. mm. of (I) existed on an area of 4 sq. mm. When the cat was anesthetized with Na barbital, (I) induced not generalized, but focal seizures at an opposite fore-leg.

I. TYUMA (Chem. Abstr.)

Changes in Serum Proteins after Brain Operations and Other Procedures Applied to the Central Nervous System. Schmidt, C., et al. [*Deut. Z. Nervenheilk.*, **170**, 119 (1953).]

The concentrations of total protein (I), albumin (II), and α-, β-, and γ-globulin (II) in the blood plasma were determined before and at several times after brain operations in 11 patients (group A), and before and after less drastic procedures (e.g. ventriculogram) in 6 patients (group B). In group A the average (I) and (II) concentrations decreased, and the (III) concentrations tended to increase after operation. In group B there was little or no change in (I), but (II) and (III) tended to change as in group A after the application of procedures to the central nervous system.

WARREN M. SPERRY (Chem. Abstr.)

Dextrin Conversion in Brain Tissue. Rashba, O. Y. [*Ukrain. Biokhim. Zhur.*, **21**, 247 (1949).]

The presence of amylase (I) in brain tissue has been previously demonstrated. It was also shown that the action of phosphorylase (II) is basically that of a polysaccharide (III) synthesizer. It became desirable to establish the ways in which primary breakdown of (III) occurs in the simultaneous presence of (I) and (II) in brain tissue. Brain tissue (II) was obtained by cold extraction with distilled H_2O. Dextrin was prepared by the action of purified brain on glycogen of rabbit liver and on amylodextrin of potato starch. Following incubation of the reacting mixtures, determinations were made of (III), inorganic P, and in some instances of glucose-1-phosphate (IV). A study was made of the synthesizing action of (II) by adding the dextrins as priming agents, as well as of the phosphorolytic action of these dextrins. It appeared that in both instances dextrins serve as suitable substrate for the action of (II). Results of (I) reactions at various stages of the experiments indicate that brain tissue (II) has an affinity for dextrins down to those of smallest mols. It is, therefore, thought that the hypothesis of simultaneous action of (I) and (II), utilizing the same substrate, appears probable, although it still remains unknown whether the two act at different foci of the same mols. The conversion of dextrins may take place as a result of the action of (I), forming maltose and glucose, as well as a result of the action of (II), forming (III) and (IV). The dextrins arising from the action of brain tissue (II) are also being converted through the simultaneous action of (I). The intermediate products in both reactions are, therefore, in part the same.

B. S. LEVINE (Chem. Abstr.)

The Enzymic Synthesis of Polysaccharides of the Brain. Khaikina, B. I., and Goncharova, K. O. [*Ukrain. Biokhim. Zhur.*, **21**, 239 (1949).]

Phosphorylase of the brain of the rabbit is highly active in polysaccharide synthesis and is independent of any external priming influences. However, the addition of appropriate enzymes increases the original synthesis. At pH 6·2 polysaccharides of the type of glycogen are synthesized; at pH 5·7 starch type. Time and pH are of considerable importance. Iodine coloration experiments indicate that in the brain (of the rabbit), in addition to phosphorylase, which synthesizes polysaccharides of the starch type, there is an enzyme capable of converting starch into a polysaccharide of a branching structure and which is named starch glycoisomerase (I). Phosphorylase and (I) can be isolated by fractional precipitation with $(NH_4)_2SO_4$.

B. S. LEVINE (Chem. Abstr.)

Electroencephalographic Modifications During Anoxemia and Variations under the Influence of Certain Substances. Tabusse, L., et al. [*J. physiol.*, **44**, 331 (1952).]

Subjects were given a gas mixture containing 7·5 per cent O in N. Electroencephalographic (EEG) changes appeared after a latent period of variable duration depending on the speed and intensity of the hypoxia and on the resistance of the subject. The paradoxical effect of O administration at this time was noted by the persistence or accentuation of the EEG changes for several seconds. A respiratory stimulant and glucose caused delay in appearance of EEG changes.

HERMANN I. CHINN (Chem. Abstr.)

Cerebral Arteriography with Sodium Acetrizoate (Urokon Sodium 30 per cent). Seaman, William B., and Schwartz, Henry G. [*Arch. Surg.*, **67**, 741 (1953).]

The results indicate this to be a satisfactory medium for cerebral arteriography.

JOHN T. MYERS (Chem. Abstr.)

Effect of Hypothalamic Stimulation on the Adrenaline Secretion of the Adrenal Glands in Cats. Suzuki, Tatsuji and Arai, Tsutomu. [*Tohoku J. Exptl. Med.*, **58**, 105 (1953).]

In cats, anesthetized with evipal, the hypothalamus was stimulated electrically with a frequency of 20 cycles/sec. and a duration of 60 seconds. Blood was collected from the adrenal vein. Stimulation of the ventro-medial and ventro-lateral portion caused an abrupt rise in blood pressure and a corresponding increase in adrenaline secretion from 0·03–0·1 to 0·5–5 γ/kg./min. The secretion rate of adrenaline fell to normal soon after the removal of the stimulus.

J. D. TAYLOR (Chem. Abstr.)

Cholinergic and Inhibitory Synapses in a Central Nervous Pathway. Eccles, J. C., et al. [*Australian J. Sci.*, **16**, 50 (1953).]

The depression of excitability of cat spinal motoneurones when adjacent motoneurones were activated by antidromic impulses was studied by recording intracellular potentials. Evidence is presented that the depression is produced by inhibitory synaptic activity through interpolated interneurones which are excited cholinergically by the motoraxon collaterals. The cholinergic mechanism was supported by experiments with drugs. The repetitive interneuronal response to an antidromic impulse was not affected by d-tubocurarine chloride

(1 mg/kg. body weight) and only moderately diminished by atropine sulfate; but 0·1 mg./kg. of dihydro-β-erythroidine hydrobromide, by blocking the action of acetylcholine, caused a prolonged depression of rhythmic response. Similarly, 1 mg./kg. of prostigmine bromide had no effect; but 0·1 mg./kg. of eserine sulfate or the dimethylcarbamate of 3-hydroxy-2-dimethylaminomethylpyridine dihydrochloride, by inactivating cholinesterase, greatly prolonged the repetitive discharge. Acetylcholine chloride (threshold dose 8 γ) evoked a series of discharges from an interneurone that was also activated repetitively from the motor-axon collaterals. Prior injection of eserine sulfate increased 10-fold, while dihydro-β-erythroidine hydrobromide decreased 10-fold the response to a given dose of acetylcholine.

J. F. KEFFORD (Chem. Abstr.)

Brain Potassium Exchange in Normal Adult and Immature Rats. Katzman, Robert and Leiderman, P. Herbert. [*Am. J. Physiol.*, **175**, 263 (1953).]

Sixty-eight normal adult male rats were injected intraperitoneally with K^{42}. The animals were killed at intervals of 4, 16, 39, 54, and 72 hours by decapitation, and plasma and brain activity and total K were measured. The K influx and outflux were calculated from a general exchange equation. The influx of K into the brain of normal adult rats was 2·89 meq./kg./hr.; the outflux rate 3·64 meq./kg./hr. and the influx/outflux ratio 0·80. Since a steady state occurs, the outflux must be equivalent to influx. Therefore 20 meg. K/kg. of wet brain is not exchangeable with K^{42}. The influx in 4- and 15-day-old animals is 3·9 meq./kg./hr., and in 35-day-old animals the influx is 3·1 meq./kg./hr. All brain K was exchangeable in 4-, 15-, and 35-day-old rats. Brain K exchange in older rats is similar to that of normal young adults.

E. D. WALTER (Chem. Abstr.)

Glycerylphosphorylethanolamine in Rat Brain. Ansell, G. B., and Norman, Joyce M. [*Biochem. J.*, **55**, 768 (1953).]

Glycerylphosphorylethanolamine (I) is present in the acid-solution P fraction of rat-brain tissue (2·3 mg. per cent) prepared from frozen material. From experiments with injected P^{32} it is concluded that (I) is not an in vivo breakdown product of phosphatidylethanolamine (II). Radioactive (I) was synthesized by minced rat brain, but in vitro synthesis of (II) was not accomplished.

S. MORGULIS (Chem. Abstr.)

Effect of Metabolic Inhibitors on Respiration and Glucolysis in Electrically Stimulated Cerebral-Cortex Slices. Heald, P. J. [*Biochem. J.*, **55**, 625 (1953).]

Brain cortex slices in vitro may show increased O uptake, increased glucolysis, increased levels of inorganic phosphate and a decreased concentration of creatine phosphate which parallel those produced under similar conditions in vivo. Iodoacetate, in concentrations which had little effect upon stimulated O uptake, depresses the stimulated accumulation of lactic acid due to a lowered rate of lactic acid production. NaF has similar effects except that lactic acid production is not lowered at concentrations of F which suppress stimulated O uptake. Neither iodoacetate nor NaF at concentrations which reduce stimulated oxidation of glucose, decrease the stimulated oxidation of lactate. Up to 0·01 M malonate decreases stimulated O uptake and increases stimulated lactic acid production, while the unstimulated response is unaffected; 0·1 M malonate suppresses unstimulated O uptake and increases aerobic glucolysis. Malonate up to 0·01 M has no effect on electrically stimulated lactate oxidation.

S. MORGULIS (Chem. Abstr.)

Accumulation of Citrate During Oxidation of Pyruvate by Breis and Slices of Pigeon Brain. Coxon, R. V. [*Biochem. J.*, **55**, 545 (1953).]

The oxidation of pyruvate by breis and slices of pigeon brain, is associated with an accumulation of citrate. Of the pyruvate metabolized by breis about 20 per cent undergoes only oxidative decarboxylation to acetate, 10 per cent undergoes anaerobic dismutation to lactate, while 67 per cent is completely oxidized to CO_2 and H_2O, leaving 3 per cent (estimated 2–4 per cent) for the formation of citrate.

S. MORGULIS (Chem. Abstr.)

Study of the Steroids of the Brain by the Chromatographic Method. Polyakova, N. M. [*Doklady Akad. Nauk. S.S.S.R.*, **93** (1953).]

Human brain tissues (white and gray matter, separately) after saponifying with alcohol KOH and extraction with Et_2O was subjected to chromatographic separation on Al_2O_3 using $(CH_2Cl)_2$ solvent, with elution of mechanically separated portions with MeOH. The zones were detected by the fluorescence method. The white matter contains 4·2 per cent unsaponifiable matter, the gray 1·26 per cent (14 per cent and 8 per cent on dry basis). The steroids comprise 90 per cent of the former and 85 per cent of the latter. The products contain various oxidation products of steroids with double bonds in the B ring. In addition, unidentified nonsteroid substances with low m.p. were isolated. The results are: the gray matter contains 0·02 per cent oxidation products of steroids, 48 per cent isomers of cholesterol, 36·8 per cent cholesterol, 0·15 per cent 7-hydroxycholesterol; the white matter, respectively, 0·02, 47·3, 45·5 and 0. The 7-hydroxy derivative was identified spectrographically.

G. M. KOSOLAPOFF (Chem. Abstr.)

Enzyme Activities of Nerves. I. Cholinesterase Activities in Various Parts of the Human Brain. Goto, Juya. [*Nisshin Igaku*, **37**, 434 (1950).]

Isolated tissues of the human brain were homogenized in Ringer solution (pH 7·4), and the cholinesterase (I) activities of these homogenates were determined with a Warburg apparatus at 37° using 0·015 M acetylcholine as the substrate. The (I) activity in the human brain was 0·5–200 cu. mm. Co_2/mg. dry wt. tissue/60 minutes. The activities in various parts of the brain were listed. The distribution of (I) was independent of age or sex. The (I) activity in the medulla was less than one-fifth of that in the cortex. The (I) activities in the brain of the rat, rabbit, and dog were different from each other, but were the same in the same kind of animals.

TETSUO KONO (Chem. Abstr.)

Biochemical Researches on the Brain and Some Practical Applications of the Results Attained. Naka, Shuzo. [*Kyushu Mem. Med. Sci.*, **3**, 203 (1953).]

A review with 35 references.

E. P. HALPERN (Chem. Abstr.)

Determination of Largactil in Biological Liquids Passage in the Animal Organism. Durost, Paul and Pascal, Suzette. [*Ann. pharm. franç.*, **11**, 615 (1953).]

Largactil is 3–chloro–(dimethylamino–3–propyl)–10–phenothiazine and used as an anesthetic of long action. It gives a red colour with H_2SO_4, red-orange with H_2SO_4 and CrO_3, dark wine colour with $PdCl_2$, and a pale yellow precipitate with NaOBr. The free compound can be extracted from blood with Et_2O and estimated with the H_2SO_4, reaction. If both the free and the conjugated compounds are to be determined the blood is subjected to hydrolysis with HCl at 100° and subsequently extracted. Urine is extracted after the addition of 2 cc. 20 per cent Na_2CO_3 solution to 20 cc. urine. Hydrolysis can be effected by refluxing with an equal volume of 20 per cent NaOH or by boiling 20 cc. with 16 cc. HCl. Single doses of 0·25 g. per kg. of largactil given orally or subcutaneously are well tolerated by rabbits but oral doses of 0·4 to 0·5 g. cause death in 24 to 48 hours. The concentration in the blood after various levels and routes of administration does not exceed 4–6 mg. per 1. Only 6–8 per cent appears in the urine which suggests a far-reaching destruction in the organism.

A. E. MEYER (Chem. Abstr.)

Recent Advances in Acetylcholine. Okinaka, Shigeo and Yoshikawa, Masaki. [*Nisshin Igaku*, **37**, 415–24, 467 (1950).]

A review, dealing mainly with the effects of various conditions on and the mechanism of acetylcholine biosynthesis, and the role it plays in the nervous stimulation. 172 references.

M. NAKAMURA (Chem. Abstr.)

Recent Advances in Cholinesterase. Okinaka, Shigeo and Yoshikawa, Masaki. [*Nisshin Igaku*, **37**, 1 (1950).]

A review, dealing with enzymic, physiological, pharmacological and clinical aspects of cholinesterase. 169 references.

M. NAKAMURA (Chem. Abstr.)

Observations on Brain Phosphatases. Gordon, J. J. [*Biochem. J.*, **55**, 812 (1953).]

The pyrophosphatase (PP-ase) and adenosinetriphosphatase (ATP-ase) of rat-brain homogenates lose activity on dialysis and both can be activated by cysteine. The 2 activities can be separated by fractionation with $(NH_4)_2SO_4$ or EtOH. In respect to (PP-ase), highly nucleated regions are generally much more active than the conducting regions; cerebellar cortex is much more active than cerebral cortex (PP-ase) activity is strongly inhibited by metal salts, mapharside, HCHO and suramin, most of which have relatively little effect on (ATP-ase) activity. It is concluded that (PP-ase) and (ATP-ase) are different systems in brain.

S. MORGULIS (Chem. Abstr.)

Glycogen in the Animal Brain. Palladin, A. V., and Khaïkina, B. I. [*Ukrain. Biokhim. Zhur.*, **22**, 462 (1950).]

In dog and rabbit brain, glycogen was determined on freeze-dried material homogenized in acetate buffer at pH 6. Glucose–1–phosphate + buffer + enzymic preparation from the brain was incubated for 60 minutes at 37°. Enzymic action was blocked by addition of CCl_3–COOH. Polysaccharide synthesis was estimated by the increase in inorganic P, and from iodine coloration. Phosphorylase activity involved in the synthesis was estimated by the amount of P split from added glucose–1–phosphate, expressed in per cent P remaining. Enzymic activity was estimated with and without the addition of glycogen as a primer. P was determined by the ordinary procedure, glucose–1–phosphate by enzymic procedure, and glycogen by the method of Kerr. The enzyme activity which results in synthesis of polysaccharides, including glycogen substrate, is about the same in the separate brain portions as for the total brain; this indicates that glycogen is synthesized in various portions of the brain. Glycogen was found also in the cortex, caudate nucleus, thalamus, cerebellum, and medulla oblongata. More glycogen was found in the cerebral cortex than in any other part of the brain. Glycogen synthesis is possible in different portions of the central nervous system of normal, as well as of pathological, animals. The enzyme system that causes synthesis of polysaccharides is highly active, and a considerable quantity of glycogen occurs in those portions of the brain that are characterized by high physiological activity. Failure of others to find glycogen in the central nervous system is attributed to postmortem decomposition of glycogen by amylase.

CLAYTON F. HOLOWAY (Chem. Abstr.)

Investigation of the Enzymic Activity of Different Portions of the Brain. Kometiani, P. A., and Klein, E. E. [*Ukrain. Biokhim. Zhur.*, **22**, 410 (1950).]

Cl was determined according to Sandrow; acetylcholine according to Feldberg adrenaline according to Shaw as modified by Utevskii and Buton; succinic dehydrogenase activity according to Warburg, as modified by Quastel and Wheatley; succinic oxidase activity by O_2 absorption after succinate addition, O_2 being measured manometrically; cholinesterase activity manometrically in the Warburg apparatus; amine oxidase manometrically as described by Blashko *et al.*; glutamic dehydrogenase by O_2 absorption in a Warburg respirometer according to Edlbacher and Wiss. In 9 bovine brains average values for dry matter, Cl, intracellular water, and extracellular water, respectively, were: white matter of the cerebrum 31·8 per cent, 1·39 mg./g., 30·2 per cent, and 38·0 per cent; gray matter of cerebrum 17·9 per cent, 1·66 mg./g., 36·9 per cent, and 45·2 per cent; cerebellum 21·0 per cent, 1·47 mg./g., 39·0 per cent, and 40·0 per cent; thalamus 27·7 per cent, 1·36 mg./g., 36·3 per cent, and 36·0 per cent; medulla 30·3 per cent, 1·37 mg./g., 32·8 per cent, and 37·1 per cent. Water distribution between extra- and intra-cellular phases of brain tissue was calculated on the assumption that all the Cl is in the extracellular phase; thus the calculation is only approximate, since some Cl is intracellular. Succinic dehydrogenase and succinic oxidase activities in microliters of gas/mg. of dry weight tissue/hour, are: lobar white matter 7·2, 0·8; lobar gray matter 24·8, 4·0; cerebellum 24·3, 3·8; thalamus 15·0, 2·6; medulla 11·5, 2·1. The ratios of intracellular dry substance to intracellular water are 0·47 for lobar white matter, 0·22 for gray matter, 0·26 for cerebellum, 0·38 for thalamus, and 0·43 for medulla. This ratio gives a conception of the quantity of protoplasm and the extent of its water supply; the data indicate that the activity of oxidative enzymes depends upon the amount of protoplasm and its water content, and that the intracellular phase possesses the greater enzymic activity which contains the more water. Cholinesterase activity decreases in the order lobar gray matter > cerebellum > thalamus > medulla > lobar white matter; which is the same sequence as with succinic dehydrogenase and succinic oxidase. It is inversely proportional to the ratio of dry substance to intracellular water. Adrenaline content in γ/g. dry substance, and amine oxidase activity (in microliters O_2 consumed/mg. dry substance/hr.), respectively are: lobar white matter 0·78, 1·7; lobar gray matter 1·86, 7·0; cerebellum 1·08, 6·9; thalamus 1·54, 2·6; medulla 0·99, 1·9. In peripheral nerve, most of the acetylcholine is intracellular; most of the adrenaline, extracellular. This is explained by assuming that acetylcholine is intracellularly synthesized, and adrenaline is brought to the cell. Of all amino acids, oxidative deamination of glutamic acid is most intense in the brain. Glutamic acid is oxidized in the brain by glutamic dehydrogenase, in the presence of codehydrase 1, diaphorase, the cytochrome system, adenosinetriphosphate, and pyridoxal. Glutamic dehydrogenase activity in microliters O_2 consumed/hour/mg. dry tissue: lobar white matter 0·09, lobar gray matter 0·59, cerebellum 0·58, thalamus 0·23, medulla 0·18. Glutamic dehydrogenase appears to be a more characteristic enzyme for nerve-cell formation than any of the other enzymes studied.

CLAYTON F. HOLOWAY (Chem. Abstr.)

Electrophoretic Studies of Cerebrospinal Fluid. Steger, J. [*Deut. Z. Nervenheilk.*, **171**, 1 (1953).]

The proteins (I) of normal and pathological CSF were concentrated by dialysis and subjected to electrophoresis. The V fraction concentration was higher in normal ventricular than in cysternal or lumbar CSF, but the ratio of the sum of the V and albumin fractions to the globulin was relatively consistent. Pathological changes in the (I) pattern are described.

WARREN M. SPERRY (Chem. Abstr.)

Glucose in the Cerebrospinal Fluid of Normal Persons and Patients with Neurosyphilis. Daza Plata, C. [*Rev. fac. med., Univ. nacl. Bogota.*, **21**, 359 (1953).]

The glucose content in 123 normal cerebrospinal fluids was 0·071–0·080 per cent. The same values were observed in 77 cases of neurosyphilis.

F. FROMM (Chem. Abstr.)

Cortisone and Hydrocortisone in Cerebrospinal Fluid. Baron, D. N., and Abelson, D. [*Nature*, **173**, 174 (1954).]

Cerebrospinal fluid was extracted and chromatographed. In 5 out of 7 samples, doubtful traces of cortisone (I) and hydrocortisone (II) were identified. In 2 pooled extracts, representing 500 ml. each of fluid, (I) and (II) were isolated in concentrations of 0·1–0·2 γ per cent and 0·2–0·4 γ per cent, respectively. Abstract identification was not done.

LEO LUTWAK (Chem. Abstr.)

Cholinesterase. III. The Cholinesterase of Cerebrospinal Fluid in Various Diseases. Okinaka, Shigeo, et al. [*Tohoku J. Exptl. Med.*, **58**, 133 (1953).]

Cholinesterase (I) activity in the cerebrospinal fluid (II) of 140 patients with various nervous diseases was determined manometrically with the Warburg app. In 10 normal subjects (I) averaged 16·9 (range 14·5–19·0) cu. mm. CO_2/ml. (II)/30 minutes. The value of (I) was lower in (II) than in serum or brain tissue and was independent of any change in the serum value. Increased activity of (I) was found in tuberculous meningitis and tumor of the brain and spinal cord. Decreased activity was found in poliomyelitis, progressive paralysis, and epilepsy. No abnormal activity was found in flaccid and spastic hemiplegia following cerebral hemorrhage, paralysis agitans, chorea minor, spastic spinal paralysis, myasthenia gravis, myotonia congenita, progressive muscular dystrophy, polyneuritis, syringomyelia, herpes zoster, and diabetes mellitus.

IV. The Relation between Cholinesterase of Basal Ganglia and Liver Disease. Okinaka, Shigeo, et al. [*Ibid.*, 139 (1953).]

The cholinesterase activity in the basal ganglia was not influenced by ordinary liver disease in 14 patients.

J. D. TAYLOR (Chem. Abstr.)

Pyruvic Acid Content of Cerebrospinal Fluid and its Diagnostic Significance. Lasch, Fritz. [*Klin. Wochschr.*, **31**, 941 (1953).]

The normal pyruvic acid content of cerebrospinal fluid is around 1 mg. per cent, the same as in serum or slightly higher. In severe diseases of the central nervous system it rises in the cerebrospinal fluid, but not in the serum.

ERICH HEFTMANN (Chem. Abstr.)

Formation, Flow, and Reabsorption of Cerebrospinal Fluid in Man. Sweet, Wm. H., and Locksley, Herbert B. [*Proc. Soc. Exptl. Biol. Med.*, **84**, 397 (1953).]

By use of isotopic tracers it was shown that water and electrolytes enter the cerebrospinal fluid (CSF) rapidly both in the ventricles and throughout the subarachnoid space. The formation of (CSF) is thus not confined to the choroid plexus. Water and electrolytes leave directly into the blood at roughly similar rates; this occurs both in the ventricles and the subarachnoid space. (CSF) does not suddenly come into being at any point with all its constituents in their proper ratios, but each constituent is exchanging with blood at its own characteristic rate. Protein is absorbed largely from the subarachnoid space, presumably from the arachnoid villi. The villi thus play a role in the (CSF) system analogous to the lymphatics of the general circulation. The net amount of new (CSF) elaborated per day in the ventricles is probably about 10–20 cc. in man.

L. E. GILSON (Chem. Abstr.)

2. Pharmacology and Treatment

Treatment of Acute Heroin Intoxication with Nalorphine (Nalline) Hydrochloride. Strober, M. [*J. Am. Med. Assoc.*, **154**, 327 (1954).]

The toxic effects of heroin, and many other narcotics, can be reversed by the administration of nalorphine.

EDWARD J. VAN LOON (Chem. Abstr.)

Experimental Anticonvulsive Activity of N-benzyl-β-chloropropionamide. Quevauviller, A., and Garcet, S. [*Thérapie*, **8**, 749 (1953).]

Experimental results of Harned *et al.* are confirmed.

GEO. SAG (Chem. Abstr.)

Barbiturates in General Medicine and in Psychiatry. Le Mappian, M. [*Semain hop. Paris*, **30**, 161 (1954).]

A review on barbiturates.

GEO. SAG (Chem. Abstr.)

Epilepsy Treatment with 5-phenyl-5-ethylhexahydropyrimidine-4, 6-dione. Beley. [*Semaine hôp., Paris*, **29**, 3463 (1953).]

Mysoline 1·25–1·50 g./day had anticonvulsive effect without hypnotic activity. Evolution of white counts during the cure is given for 17 cases.

GEO. SAG (Chem. Abstr.)

Effect of Aconitine on the Metabolism of Brain Tissue. Sorm, F., and Berankova, Z. [*Chem. Listy*, **48**, 80 (1954).]

The influence of aconitine upon metabolism of the gray matter was followed. Low concentrations of aconitine (0·02–0·2 mg. per cent) stimulate considerably the metabolism. Higher concentrations first stimulate, then inhibit metabolism. The stimulation which is specific for the brain tissue is ascribed to the activation of the O bond.

M. HUDLICKY (Chem. Abstr.)

Pharmacological Properties of Tetraethylthiuram Disulfide (Antubuse) and Certain of its Derivatives. Czyzyk, A. [*Polska Akad. Umiejetnosoi, Rozprawy Wydziatu Lekarski,* **12,** *No. 11, 38 pp.* (1951).]

Tetraethylthiuram disulfide (I) produces supersensitivity to EtOH. (I) was prepared by the method of Grodski, a yellow powder, insoluble in water, moderately soluble in alcohol, very soluble in $CHCl_3$, m. 70°. (I) was administered in suspension. The work of Larsen *et al.* was repeated. AcH level in the blood reaches its highest values 3–4 hours after administration by stomach of EtOH, whereas EtOH blood level falls after 1–3 hours. (I) increases EtOH toxicity for mice. EtOH in blood was determined according to Widmark. EtOH rabbit blood level is not affected by stomach administration of (I), nor was according to Stotz. Blood sampling by cutting the rabbit marginal vein gave fluctuating results, depending upon rapidity of blood outflow, the slower the flow, the less the blood AcH value; necessity for rapid blood sampling is emphasized. After administration of EtOH+(I), AcH blood level is 5–10 times higher than when EtOH is administered alone. After administration of EtOH, increased O consumption and increased CO_2 evolution were noted (after 4 hours, 37·2 per cent for O_2 and 26 per cent for CO_2). Respiratory quotient for EtOH was 0·7. Dosage was 1·5 g. abs. EtOH/kg. Change occurred only during 2–4 hours after EtOH. With a dosage of 2·0–3·0 g. (0·5 g./day) of (I) to the stomach+1·5 g. abs. EtOH/kg. dosage there was no increased O consumption, and the conclusion is reached that EtOH metabolism is somewhat hindered, and at the AcH stage, since AcH accumulates. Only at 0·5 g. (I) daily dose for rabbits is there noted increased AcH in rabbit blood after administration of EtOH, decrease in gas exchange being observed. (I) in direct contact with cells (rat-liver homogenate in Warburg app.) had no noticeable effect, nor did (I) show any increase in AcH of isolated tissue. (I) may be the precursor of another substance which acts in some characteristic manner upon cellular enzymes. Tetramethylthiuram disulfide (II) and dipiperidinothiuram disulfide (III) were, respectively prepared according to Braun and Ethrenburg. (II) exhibited the same pharmacological action on animals typical for (I).

CLAYTON F. HOLOWAY (Chem. Abstr.)

Chemical Constitution and the Depression of the Central Nervous System. Mingoia, Q. [*Arquiv. biol.,* **37,** 103 (1954).]

A review.

F. FROMM (Chem. Abstr.)

Antagonists of Decamethonium Iodide at the Neuromuscular Junction. Dallemagne, M. J., and Philippot, E. [*Experientia,* **9,** 427 (1953).]

Pentamethonium iodide, tubocurarine, paludrine, and di-2-heptylamine-HCl are effective inhibitors of the neuromuscular inhibiting effect of decamethonium iodide in the cat 4,4′-Diamidinostilbene, 4,4′-diamidino-α, ω-diphenoxypentane, and monolaurate of sorbitan are less active. These compounds are histamine liberators.

D. S. FARNER (Chem. Abstr.)

The Action of Synaptotropic Substances on Certain Efferent and Afferent Structures of the Autonomic Nervous System. Konzett, H., and Rothlin, E. [*Experientia,* **9,** 405 (1953).]

A review with 167 references.

D. S. FARNER (Chem. Abstr.)

Convulsions in Young Infants as a Result of Pyridoxine (Vitamin B_6) Deficiency. Molony, C. J., and Parmelee, A. H. [*J. Am. Med. Assoc.,* **154,** 405 (1954).]

Six infants artificially fed a compound preparation developed a peculiar convulsive disorder. These seizures ceased when fed another milk formula containing adequate amounts of pyridoxine.

EDWARD J. VAN LOON (Chem. Abstr.)

Glutamic Acid in the Mental Functioning of Mentally Defective Children. De la Fuente Muniz, R., and Zuniga, M. C. [*Bol. med. hosp. infantil,* **8,** 160 (1951).]

In 28 out of 36 cases classified in the clinical categories of primary mental deficiency, mental deficiency with cerebral palsy, mongoloid mental deficiency, and mental deficiency subsequent to encephalitis, an improvement was noted in the intellectual functioning and in the personality as a whole. The doses of glutamic acid used fluctuated between 12 and 24 g., and the duration of the treatment, between 4 and 20 months. No important toxic symptoms were found. Conclusion: The glutamic acid had a favorable but limited action in the treatment of mentally retarded children.

EVA SOTO-FIGUEROA (Chem. Abstr.)

Concentration of Antibiotics in the Brain. Wellman, W. E., et al. [*J. Lab. Clin. Med.,* 43, 275 (1954).]

One of several antibiotics was given prophylactically to patients undergoing prefrontal lobotomy. At the time of operation specimens of blood, cerebrospinal fluid, and brain tissue were collected for assay. Only Neopenil (diethylaminoethyl ester hydroiodide salt of penicillin G) and Aureomycin were found consistently in significant amount in the brain tissue. Terramycin was found in the brain tissue of 3 of 4 patients.

EDWARD J. VAN LOON (Chem. Abstr.)

Inactin and Cerebral Depression. Boerle, L. A. [*Der Anaesthesist*, **3,** 6 (1954).]

Pharmacological properties of thiopental-Na and Na 5-ethyl-5-(1-methylpropyl)-2-thiobarbiturate (inactin) are compared. The latter has less hypnotic and depressant activity and stimulates the vagus less than thiopental-Na.

KARL F. URBACH (Chem. Abstr.)

The Behavior of Serum Proteases in Electroshock Treatment. Konyves-Kolonics, L., and Kovacs, B. [*Monatsschr. Psychiat. Neurol.*, **126,** 184 (1953).]

Fibrinolysin (I) activity was determined by precipitating fibrin from diluted (1:19) citrated plasma with Ca, incubating it at 37° for 24 hours in plasma, and determining the amount undissolved. No (I) was found in plasma from 101 mental patients before electroshock (II), whereas after (II) there was complete fibrinolysis in 51 and partial in 11. The (I) activity had disappeared by 15 minutes after (II). Tryptase, determined by the method of Schmitz, increased after (II) in patients whose plasma (I) increased, but remained the same when there was no (I) activity.

WARREN M. SPERRY (Chem. Abstr.)

Distribution of Chloral Hydrate in Various Areas of the Central Nervous System Under the Action of Analeptics. Kudrin, A. N. [*Fiziol. Zhur. S.S.S.R.*, **40,** 65 (1954).]

Dogs treated intravenously with chloral hydrate and various analeptics were examined after killing for distribution of the former substance in the body. The largest concentrations of the drug are found in the cerebral cortex, thalamus, and lesser amounts in the medulla and the spinal cord, blood, and spinal fluid. Analeptics (combinations of caffeine, corazole, strychnine, picrotoxin) accelerate the destruction of chloral hydrate in the organism, reduce its concentration in the brain, spinal cord tissues, and the thalamus, but increase it in the blood and spinal fluid. They also improve or hasten the waking process in the central nervous system and the animals on waking show relatively higher concentrations of chloral hydrate in the brain, spinal cord, blood and other tissues in comparison with the conditions in the narcotic state.

G. M. KOSOLAPOFF (Chem. Abstr.)

Effect of Narcotic and Convulsant on Lactic Acid, Phosphate Esters, and Acetylcholine Content of the (Rabbit) Brain. Kozawa, Shunji, et al. [*Japan. J. Pharmacol.*, **3,** 50 (1953).]

Lactic acid (I), inorganic phosphate (II), creatine phosphate (III), pyrophosphate (IV), hexose phosphate (V), free acetylcholine (VI), and total acetylcholine (VII) were determined on rabbit brain immediately after intravenous treatment with Na amytal or metrazole. Na amytal produced a 37 per cent fall in (IV) with less impressive decrease in (III) (10 per cent) and (II) (7 per cent). A 10 per cent decrease in (VII) was observed and a 6 per cent fall in (I). Metrazole produced a 24 per cent increase in (IV) with 11 per cent increases in both (III) and (V). (VI) increased 53 per cent and (I) increased 33 per cent. The authors concluded that under anesthesia glycolysis and (I) production of the cerebral cortex are depressed and (VII) content decreases slightly. In convulsive states glycolysis and (I) production are accelerated and (VII) increases.

FRANK IBER (Chem. Abstr.)

Pharmacologic Studies on a New Central Stimulant, α(2-piperidyl) Benzhydrol Hydrochloride. Brown, B. B., et al. [*J. pharmacol. Exptl. Therap.*, **110,** 180 (1954).]

The compound is a new type of central stimulant which induces a coördinated hyperactivity in experimental animals and causes changes in behavior patterns. Convulsions do not occur with less than $L.D._{50}$ doses, and the convulsions are not followed by an after-depression as are those induced by amphetamine. The drug weakly antagonizes barbiturate depression, but not the lethal action of barbiturates. Its own lethal action is poorly antagonized by barbiturates. It has little or no pressor action.

L. E. GILSON (Chem. Abstr.)

Influence of Various Narcotics on Cerebral Circulation. Tokita, N. [*Tohoku J. Exptl. Med.*, **59,** 149 (1953).]

The influence of various narcotics on the blood flow in the cortex and medulla oblongata was followed in cats by using the Schmidt and Pierson thermocouple. Bilateral ligature of the carotid arteries caused a decrease and adrenaline injections an increase in cerebral circulation. In all cases tested, the blood flow in the cortex and medulla oblongata changed simultaneously. Et_2O inhalation gave a slight decrease in blood flow which returned to normal with the cessation of the anesthesia. $CHCl_3$ and EtCl increased the blood flow, which in many cases decreased below normal levels when the anesthetic was stopped. Na amytal and Na evipal decreased the blood flow, but recovery was faster with the latter. Morphine–HCl decreased the blood flow immediately after intravenous injection.

A. DIETZ (Chem. Abstr.)

Nicotine and Neurohypophysis. Denninger, K. [*Arzneimittel-Forsch.*, **4**, 79 (1954).]

Nicotine has a well-defined influence upon the water regulation through the diencephalon-posterior hypophysis. This effect can be used for the differential diagnosis of polydipsia and may also be significant therapeutically.

K. SCHOEN (Chem. Abstr.)

Neurological Complications Following the Use of Efocaine. Nowill, Wm. K., et al. [*Arch. Surg.*, **67**, 738 (1953).]

After the administration of efocaine transverse myelitis occurred in 2, Brown-Sequard syndrome in 1, intercostal nerve block in 1, and sympathetic nerve block in 2 cases.

JOHN T. MYERS (Chem. Abstr.)

Effect of Electroshock Therapy on Blood Lactic Acid and Pyruvic Acid. Eiduson, Samuel, et al. [*Proc. Soc. Exptl. Biol. Med.*, **84**, 364 (1953).]

Determinations were made on blood of neuropsychiatric patients before and after extreme muscular excitation induced by electroshock therapy (EST). Blood lactic acid rose sharply to a peak of about 6 times pre-shock level within 3–5 minutes after EST and returned to normal in 1–1·5 hours. The blood pyruvic acid of all patients rose immediately after EST for 30 seconds, then fell to a minimum (2·3 mg. per cent) within 3–5 minutes and rose again to a peak 3 times the pre-shock level 20 minutes after EST. Blood glucose, Na, K, and Ca varied considerably over a 60 minute period following EST, rising and falling several times during this time interval.

L. E. GILSON (Chem. Abstr.)

Action of Hypnotic Drugs on the Carbohydrate Metabolism of the Brain. I. Formation and Utilization of Hexose Phosphates in Normal Cerebral Tissue. Etling, Nicole. [*Bull. soc. chim. biol.*, **35**, 751 (1953).]

Rat brain was shown to contain all the enzymes concerned in the first stages of phosphorylative glycolysis: phosphorylase, phosphoglucomutase, hexokinase, oxoisomerase, and phosphohexokinase.

L. E. GILSON (Chem. Abstr.)